PREPARATION, CHARACTERIZATION AND EVALUATION OF INDOMETHACIN SOLID DISPERSIONS

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Coimbatore – 641044

CERTIFICATE

This is certify that the research entitled **"PREPARATION, CHARACTERIZATION AND EVALUATION OF INDOMETHACIN SOLID DISPERSIONS"** was carried out by **Mr.VENKAT VEERENDRANADH YENIGALLA** in the **Department Of Pharmaceutics,** College Of Pharmacy, Sri Ramakrishna Institute Of Paramedical Sciences, Coimbatore, which is affiliated to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and guidance to my fullest satisfaction

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VENKAT VEERENDRANADH YENIGALLA

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ABBREVIATIONS

INM	- INDOMETHACIN
SD	- SOLID DISPERSION
PM	- PHYSICAL MIXTURE
β-CD	- β-CYCLODEXTRIN
HPβ-CD	- HYDROXY PROPYL β-CYCLODEXTRIN
KM	- KNEADING METHOD
UV	- ULTRA-VIOLET
FT-IR	- FOURIER TRANSFORM INFRA RED
TLC	- THIN LAYER CHROMATOGRAPHY
DSC	- DIFFERENTIAL SCANNING COLORIMETRY
DTA	- DIFFERENTIAL THERMAL ANALYSIS
XRD	- X-RAY DIFFRACTION
SEM	- SOLVENT EVAPORATION METHOD
DCV	- DIRECT COMPRESSIBLE VEHICLE
CO	- CO-EVAPORATION

INTRODUCTION

SOLID DISPERSION SYSTEM AND ITS HISTORICAL BACKGROUND

One of the most useful methods to overcome the inherent difficulties associated with the formulation development of a sparingly water soluble drug is to enhance the solubility of the same.

The enhancement of oral bio availability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilisation and particle size reduction have been commonly used to increase dissolution rate and there by oral absorption and bio availability of such drugs, there are practical limitations to these drugs. They have been commonly used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs. There are practical limitations to these techniques. The salt formation is not feasible for neutral drugs and synthesize of appropriate salt forms of the drugs that are weakly acidic or basic may not be practical. Even when salts are prepared, an increase in dissolution rate in gastro intestinal tract may not be achieved in many cases because of the reconversion of salts into their respective acid or base forms.

Solid dispersions have been considered as means of increasing the solubility, dissolution and absorption of poorly soluble drugs. This concept of solid dispersion was introduced by **Sekiguchi and obi**[1]. They suggested that the drug was present in a eutectic mixture in a micro crystalline state.

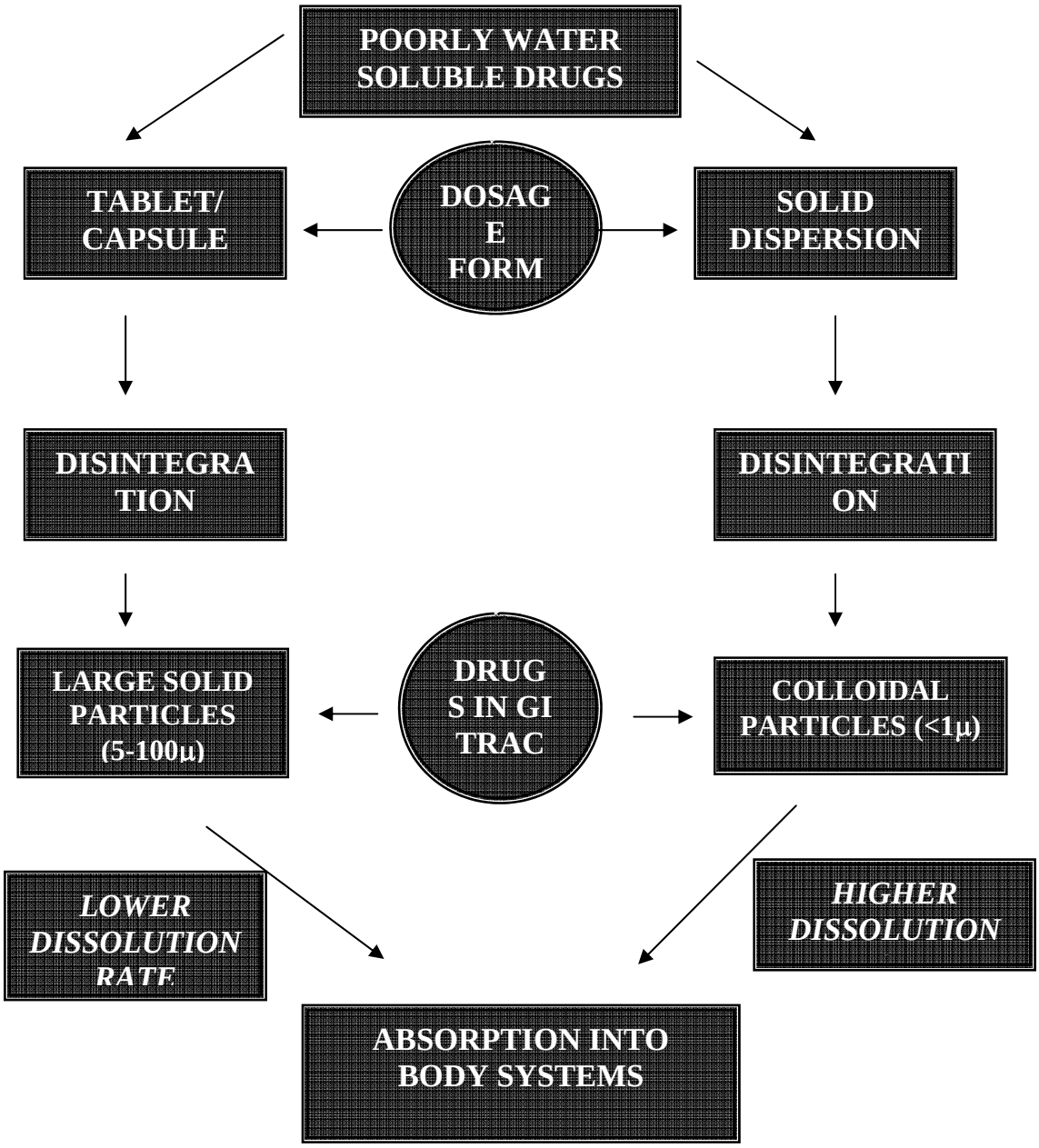


Figure no : 1 ***Schematic Representation of the bio availability enhancement of poorly water-soluble drug by solid dispersions compared with conventional tablet or capsule.***

All the drug in solid dispersion might not be necessarily present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and carrier dissolved, the drug was released as very fine and colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high.

1.1 DIFFERENT TYPES OF SOLID DISPERIONS[2]

a. Simple eutectic mixtures

Eutectic mixtures consist of two components which are completely miscible in the liquid state but only to a very limited extent in the solid state. Solid eutectic mixtures are usually prepared by rapid cooling of very fine crystals of the two components. When the preparation is dissolved in aqueous medium the carrier will dissolve rapidly, releasing very fine crystals of the drug which offers large surface area that result in improvement of dissolution and there by improved bioavailability.

b. Solid solutions

Solid solutions consist of just one phase in which drug and the carrier are in the solid state. The drug'particle size has been reduced to its absolute minimum and the dissolution rate is determined by the dissolution rate of the carrier. Thus by the judicious selection of a carrier, the dissolution rate of the drug can be increased up to several orders of magnitude.

Solid solutions can be classified according to two methods:

According to their miscibility, continuous and discontinuous solid solution. According to the way in which the solvate molecules are distributed in the solvent, substitutional, interstitional and amorphous solution.

- **Continuous solid solutions**

In continuous solid solutions, the components are miscible in all proportions. The bonding strength between the two components is stronger than the bonding strength between molecules of each of the individual component. These types of solid dispersions are not used pharmaceutically.

- **Discontinuous solid solutions**

The solubility of each of the components is limited. The strategy of solid solutions for a dosage form depends upon the mutual solubility of the two components and also the dose of the drug component.

- **Substitutional crystalline solid solutions**

The substitutional crystalline solid solutions will have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules.

- **Interstitial crystalline solid solutions**

In interstitial crystalline solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in crystal lattice.

- **Amorphous solid solutions**

In amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly with in the amorphous solvent. Using griseofulvin in citric acid. **Chiou and Reigelmann[3]** were the first to report the formation of an amorphous solid solution to improve the dissolution properties. Other carriers used in early studied included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG) and various cellulose derivatives are also used.

- **Glass solutions**

Glass solutions are a homogenous system in which the solute dissolves in a glassy solvent. A glass solution is a metastable form. The lattice energy is much less than a solid solution. So the dissolution of a drug in a glass solution should be theoretically faster than in solid solution.

1.2 ADVANTAGES OF SOLID DISPERSIONS

Solid dispersions of drug in solid is helpful in stabilizing unstable drugs. Many of the advantages claimed for SD derived from their rapid dissolution rate. The increased rate of Nitrazepam from their Citric acid dispersion produce increase in the rate and extent of absorption.

Solid dispersions of drug in carrier offers solubility potential for sustained release polymeric materials e.g., copolymer C.A. II(R), a vinyl acetate copolymer with 11% Erotonic acid or Eudragit (R) have been co evaporated or fused to provide sustain release of Codeine.

The PEGs may protect certain drugs e.g. cardiac glycosides against the decomposition by saliva and allow buccal absorption.

Solid dispersions technology may also be used to solidify drugs e.g. Clofibrate and benzyl benzoate.

Finally the unique technique was claimed for Prednisolone-urea dispersion when incorporated in ointment base an increased diffusion of steroid from the ointment was obtained.

1.3 LIMITATION OF SOLID DISPERSION SYSTEMS

a. Its method of preparation
b. Reproducibility of its physicochemical properties
c. Its formulations into dosage forms
d. The scale up of manufacturing processes and
e. The physical and chemical stability of drug and vehicle
f. Future aspects

Despite of many advantages of solid dispersion issues related to preparation, reproducibility, scale up and stability limited its use in commercial dosage forms for poorly water soluble drugs. Successful development of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface active and self-emulsifying carriers with relatively low melting points. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and as a result the bio availability of solid dispersions are not expected to change

significantly during scale up. For this reason popularity of the solid dispersions to solve difficult bio-availability issues with respect to poorly water soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system has an advantage, over the other commonly used bio-availability enhancement techniques such as micronization of drugs and soft gelatin encapsulation.

Research should also be directed towards identifications of vehicles or excipients that would retard or prevent the crystallisation of drug from super saturated systems. Attention must also be given to any physiological effects of carriers used.

Physical and chemical stability of both drug and the carrier in a solid dispersion are major development issues, as exemplified by the recent withdrawal of Ritongx capsules from the market, so future research needs to be directed to address various stability issues.

Although, as mentioned earlier, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports scale up of the technology. Further studies on scale up and validation of the process will be essential.

1.4 CARRIERS USED FOR SOLID DISPERSIONS[4,5]

a. Poly ethylene glycols

Poly ethylene glycols are polymers of ethylene oxide a molecular weight usually falling in the range of 200 - 300,000. For solid dispersions PEGs with a molecular weight of 1500 - 20,000 are usually used. As the molecular weight increases, so does the viscosity of PEG. Their solubility in water is generally good but decreases with molecular weight. A particular advantage of PEGs for the formation solid dispersions is that, they have good solubility in many organic solvents.

b. Poly vinyl pyrrolidine (PVP)

Polymerization of Vinyl pyrrolidine leads to Poly vinyl pyrrolidine (PVP) of molecular weight from 2500 - 3000,000. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for solvent method. Similarly to the PEGs, the PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. The aqueous solubility of PVPs becomes poorer with increasing chain length and further much higher viscosity at a given concentration.

E.g. Poly vinyl alcohol, Poly vinyl pyrrolidine Acetate co-polymer.

c. Urea

Urea has slightly diuretic effect and its solubility in water is greater than one and it also exhibits good solubility in water and many common organic solvents. In one of the first bioavailability studies of solid dispersion, it was

shown that sulphathiazole was better absorbed in rabbits when given as eutectic with urea. Similarly Goldberg *et al* in 1966 reported faster dissolution rates of chloramphenicol when prepare with urea as carrier.

1.5 CHARACTERIZATION OF SOLID DISPERSIONS[4]

- The different methods that have been used to characterize solid dispersion are;
- Thermo analytical methods, differential thermo analysis and hot stage microscopy.
- Powder X-Ray diffraction.
- Spectroscopic methods, especially IR spectroscopy.
- Microscopic methods including polarization microscopy and scanning electron microscopy.
- Colorimetric analysis of the solution or melting enthalpy for calculation of entropy change.
- Dissolution testing.

a. Thermo analytical methods

Thermo analytical methods include all that examine a characteristic of the systems as a function of temperature. Of this, Differential scanning colorimetry is the most highly regarded method. DSC enables the quantitative detection of all process in which energy is required or produced, i.e., endothermic and exothermic phase transition. The usual method of measurement is to heat the reference and two test samples in such a way

that the temperature of two is kept identical.

If an energy requirement transition occurs in the test samples, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy or the phase transition.

Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can be also detected. Lack of a melting peak in DSC of solid dispersion indicates that the drug is present in amorphous than the crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However crystallinities of fewer than 2% cannot be generally detected with DSC.

b. X-ray diffraction

The principle behind XRD is that when an x-ray beam is applied to sample, interference bands can be detected. The angle at which interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystalline sample is reflected by a characteristic finger point region in the diffraction pattern. Owing to the specificity of the finger print, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-Ray Diffraction to differentiate between solid dispersions, in which it is partly present in crystalline form, regardless of whether the carrier is

amorphous or crystalline. However, crystallinities of under 5-10% cannot generally be detected with XRD.

c. Infra red spectroscopy

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by Infra red spectroscopy. Since not all the peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not

.d. Dissolution testing

Release rate cannot be used on a stand alone basis to determine whether a solid dispersion has been formed or not. However in conjunction with other physiochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve dissolution characteristics of the drug, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. Well designed release experiments will show whether the solubility of the drug and its dissolution rate can be enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixture can help to indicate the dissolution via solubilization and wetting which could be affected.

1.6 SOLID DISPERSION TECHNIQUES[5,6]

a. FUSION METHOD OR MELTING TECHNIQUE

This fusion or wafting method was proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. This is technically the easiest method of preparation provided the drug and the carrier are miscible in the molten state. The melted mixture is collected and solidified in an ice bath under vigorous stirring. The final mass is crushed, pulverized and sieved. This technique subsequently employed with modification of Goldberg et al to facilitate fast solidification. The homogenous melt was poured in form of a thin layer onto a ferric plate or a stainless steel plate and cooled by flowing air or water onto the opposite side of the plate. The solidified masses were stored in the dessicator at ambient temperature for hardening and ease of powdering.

Advantage

1. Simplicity and economy of process are the main advantages of this method.
2. Super saturation of a solute or a drug in a system can be often obtained by quenching of the melt rapidly from high temperature.

Disadvantage

1. Many substances, either drug or carrier may decompose or evaporate during the fusion process at high temperature.

Examples of solid dispersion prepared by this method

Solid dispersion of Acetaminophen, Griseofulvin, Primidone, Chloropropamide,Chloramphenicol,Tolazamide,Steroids,Ketoprofen, Nimuselide.

b. Solvent evaporation method(SEM)

This method involves (Tantishaiyakul et al., 1999) dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. The mass was then stored in dessicator, pulverised and sieved. Solid dispersion prepared by this technique was termed by bates et al., as Co-Precipitate. They should be more correctly be designated as “Co-evaporates”.

Advantage

1. The thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

Disadvantages

1. Higher cost of preparation
2. Difficulty in completely removing the solvent
3. Possible adverse effect of the negligible amount of solvent on the chemical stability of the drug.

Examples of solid dispersion prepared by this method

Griseofulvin-PVP, Sulfathiazole-PVP.

c. Melting solvent method

This is not a common method and is not specified in most books and journals .In this method the drug is dissolved in a suitable liquid solvent and the solution is then incorporated directly into the melt of carrier obtained below 70^{o} C with out the removal of the liquid solvent.

Advantages

1. Posses the advantages of both melting and solvent methods.

Disadvantages

1. This method is suitable only for drug whose therapeutic dose is below 50 mg.
2. Selected solvent or dissolved solution may be not miscible with the melt of the carrier.

Examples of solid dispersion prepared by this method

Solid dispersion of Clofibrate, Methyl salicylate, Benzyl benzoate, Spiranolactone, Di-α-Tocopherol acetate etc.

Table no : 1 SOLID DISPERSIONS OF THERAPEUTIC AGENTS

Drug	Carrier	Method	Type of solid Dispersion	Effect of Dissolution Rate
Triamterene	B-cyclodextrin	S, K	Not Studied	Increased
Flurbiprofen	PVP	S	Not Studied	Increased
Caffeine	Nicotinamide	M	Peritech	Increased
Chloramphenicol	Urea	M	Solid Solution	Increased
Clofibrate	PEG 6000	M, S	Not Studied	Increased
Corticosteroids	Sugars	M	Not Studied	Increased
Diazepam	PEG 4000	M	Eutectic with solid Solution	Not Studied
Griseofulvin	Succinic acid	M	Solid Solution	Increased
	PVP	S	Not Studied	Increased
	PVP-30	Spray Embedding	Solid Solution	Increased
	PEG -4000	M, S	Not Studied	Increased
	PEG -6000	M, S	Not Studied	Increased

	PEG-2000	M, S	Not Studied	Increased
	Anhydrous citric acid	M	Glass suspension	Increased
Indomethacin	PEG 6000	M	Not Studied	Increased
Methyl salicylate	PEG 6000	M,S	Not Studied	Increased
Paracetamol	Urea	M	Solid solution	Increased
Mannitol	M	Eutectic	Increased	
Primidone	Citric acid	M	Glass solution	Increased
Reserpine	PVP	S	Not Studied	Increased
	Cholanic acid	S	Not Studied	Increased
	Deoxychoilic acid	S	Not Studied	Increased
Sulfathiazole	Urea	M	Simple eutectic	Not Studied
Tolubutamide	PEG-4000	S	Not Studied	Increased
	PEG-6000	S	Not Studied	Increased
	PEG 4000+6000	M, S	Not Studied	Increased
	PEG-2000	M, S	Monoacetic	Not Studied

	PVP	S	Not Studied	Increased
	Polyoxyl 40 stearate	M, S	Not Studied	Increased
	PEG-8000	M, S	Not Studied	Increased
	PVP	S	Not Studied	Increased
	PEG-6000	S	Not Studied	Increased
	PEG-4000	M	Not Studied	Increased
Allopurinol	PVP	S	Not Studied	Increased
Benzybenzoate	PEG 6000	M, S	Not Studied	Increased

1.7 NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)[7,8,9]

The anti inflammatory, analgesic and antipyretic drugs are the heterogeneous group of compounds often chemically unrelated and share certain therapeutic action and side effects. They act primarily on the peripheral pain mechanisms but also on CNS to release pain threshold.

An ideal anti-inflammatory drug should effect only aberrant, uncontrolled inflammation by modifying response to disease but not to interfere with normal inflammation process, which is a part of the body's vital defence mechanism to its major environment insults or invading micro-organisms.

NSAIDS may be classified as

A. Non selective cox inhibitors (conventional NSAIDS)

1. Salicylates

Aspirin, Diflunisal

2. Pyrazolone derivatives

Phenylbutazone, Oxyphenylbutazone

3. Indole derivatives

Indomethacin, Sulindac

4. Propionic acid derivatives

Ibuprofen, Naproxen, Ketoprofen, Flubiprofen.

5. Arthraniic acid derivatives

Mephenamic acid

6. Aryl-acetic acid derivatives

Diclofenac

7. Oxicam derivatives

Piroxicam, tenoxicam

8. Pyrrolo-pyrrole derivatives

Ketorolac

9. Preferential cox-2 inhibitors

Nimesulide, Meloxicam, Nebumentone

10. Selective Cox-2 inhibitors:

Celecoxib, Rofecoxib, Valdecoxib

B. Analgesic-antipyretics with poor anti-inflammatory action

1. Para amino phenol derivatives: paracetamol

2. Pyrazolone derivatives: Metamizol (Dipyrone) Propiphenazone

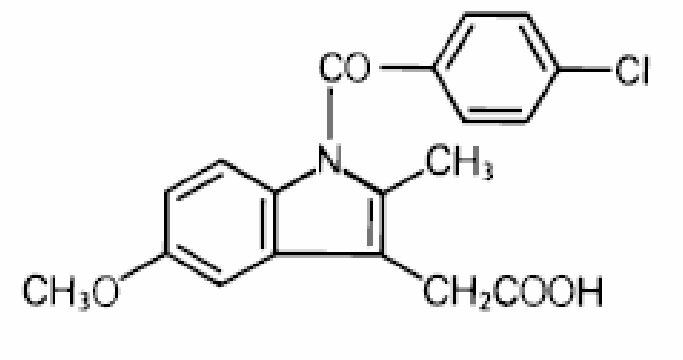
3. Benzoxazocine derivative: Nefopam.

Mechanism of Action of NSAIDs

NSAIDs are generally inhibitors of the enzymes, cyclo-oxgenase which results in the direct inhibition of the bio-synthesis of prostaglandins and thromboxanes from arachidonis acid. There are two forms of cyclo-oxygenase, COX-1, which is constructive form of the enzyme and COX-2, whuch is the form induced in the presence of inflammation. Inhibition of COX-2, is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory and anti-pyretic properties of NSAIDs, where as inhibition of COX-1 is thought to produce some of their side effects, mainly on gastro-intestinal tract. Most NSAIDs is in clinical use inhibit COX-1 and COX-2.

DRUG PROFILE

INDOMETHACIN [10,11,12,13]



Chemistry

1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H- Indole-3-acetic acid

Category

Anti-inflammatory, Analgesic

Description

White to pale yellow, crystalline powder, odourless

Molecular weight

357.79

Empirical formula

$C_{19}H_{16}NO_4Cl$

Solubility

Soluble in chloroform; sparingly soluble in ethanol (95%) and practically insoluble in water

Storage

Stored in well closed, light resistant containers

Pharmacodynamics

Mechanism of action

Indomethacin has prominent antiinflammatory and analgesic-antipyretic properties similar to those of the salicylates. Indomethacin is a more potent inhibitor of the cyclooxygenases than is aspirin, but patient intolerance generally limits its use to short-term dosing. Indomethacin has analgesic properties distinct from its antiinflammatory effects, and there is evidence for central and peripheral actions.

Pharmacokinetics and metabolism

Oral Indomethacin has excellent bioavailability. Peak concentrations occur 1 to 2 hours after dosing. Indomethacin is 90% bound to plasma proteins and tissues. The concentration of the drug in the CSF is low, but its concentration in synovial fluid is equal to that in plasma within 5 hours of administration. Between 10% and 20% of indomethacin is excreted unchanged in the urine, partly by tubular secretion. The majority is converted to inactive metabolites.

Half life

The half-life in plasma is variable, perhaps because of enterohepatic cycling, but averages about 2.5 hours.

Therapeutic uses

Indomethacin is effective for relieving joint pain, swelling, and tenderness, increasing grip strength, and decreasing the duration of morning stiffness.

- It is estimated to be approximately 20 times more potent than aspirin.
- It suppresses inflammation in a manner similar to steroids, but less side effects of sedation.
- They are widely used for the treatment of inflammatory disorders and painful conditions such as rheumatoid arthritis, gout, bursitis, painful menstruation, and headache

Drug Interactions

Indomethacin does not directly modify the effect of warfarin, but platelet inhibition and gastric irritation increase the risk of bleeding, concurrent administration is not recommended. Indomethacin antagonizes the natriuretic and antihypertensive effects of furosemide and thiazide diuretics and blunts the antihypertensive effect of β-receptor antagonists, AT_1 receptor antagonists, and ACE inhibitors.

Adverse Effects

A very high percentage (35% to 50%) of patients receiving usual therapeutic doses of indomethacin experience untoward symptoms, and about 20% must discontinue its use because of the side effects. Most adverse effects are dose-related.

Gastrointestinal complaints are common and can be serious. Diarrhoea may occur and sometimes is associated with ulcerative lesions of the bowel. Underlying peptic ulcer disease is a contraindication to indomethacin use. Acute pancreatitis has been reported, as have rare, but potentially fatal, cases of hepatitis.

POLYMER PROFILE

CARRIERS USED IN THIS PROJECT

SELECTION OF A SUITABLE CARRIER[14]

A carrier chosen for the solid dispersions is designed to increase the dissolution rate of drugs should meet the following requirements

I. Freely soluble in water with intrinsic rapid dissolution properties.

II. Should be non toxic.

III. Pharmacologically inert.

IV. Chemically compatible with drug.

V. Carrier should be soluble in a variety of organic solvents.

VI. Melting point not much higher than the drug.

The carriers used in the study are β-cyclodextrin and hydroxyl propyl β-cyclodextrin.

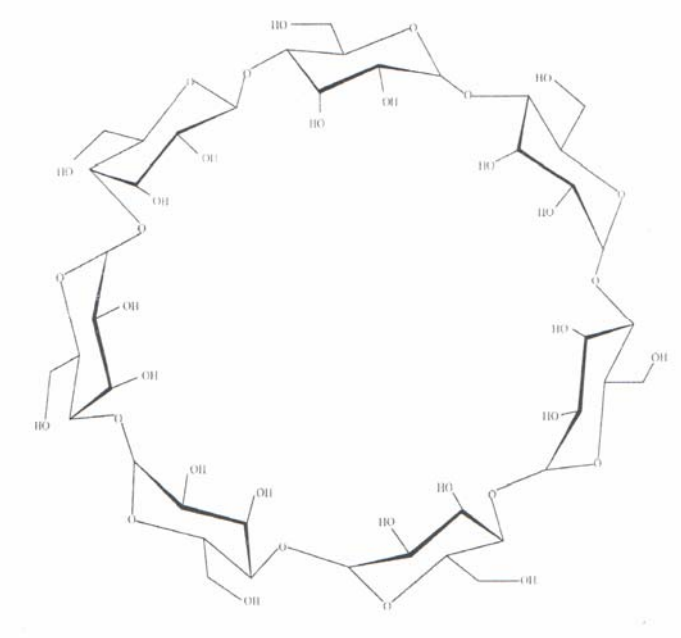
β-CYCLODEXTRIN[15,16,17]

Synonyms: beta-cycloamylose, beta-dextrin, Cycloheptaamylose, Kleptose, Cavamax W7 pharma, Cyclomalto- Heptose

Appearance : white crystalline powder

Empirical formula : $C_{42}H_{70}O_{35}$

Molecular structure



Molecular weight : 1135

Melting point : 255-265^{o}C

Solubility: 1 in 200 parts of PEG at room temperature 1 in 50 parts of water at 20^{0}C Insoluble in acetone , ethanol (95%) and methylene Chloride

Compressibility : 21.0-44.0%

Density(Bulk) : 0.523 g/cm^{3}

Density(Tapped) : 0.754 g/cm

Particle size distribution : 7.0-45.0 µm

Specific rotation at (25^{0}C) : +162.0

Surface tension: 71 m N/m (71 dynes/cm)

Chemical name and CAS Registry Number : β-cyclodextrin [7585-39-9]

Empirical formula : $C_{42}H_{70}O_{35}$

Functional category : Solubilizing agent, stabilizing agent

STABILITY AND STORAGE CONDITION

β-cyclodextrin and other cyclodextrins are stable in a solid state if protected from high humidity. Cyclodextrins should be stored in a tightly closed container, in a cool and dry place.

INCOMPATIBILITIES

The activity of some anti microbial preservatives in aqueous solution can be reduced in presence of cyclodextrins.

APPLICATION IN PHARMACEUTICAL TECHNOLOGY

Cyclodextrins are bucket like or cone like toroid molecules, rigid structure and a central activity, the size of which varied according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic, due to the arrangement of the hydroxyl groups with in a molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule with in a cavity,forming an inclusion complex. Cyclodextrin may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements of dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability.

I. β-cyclodextrin is considered to be non toxic when

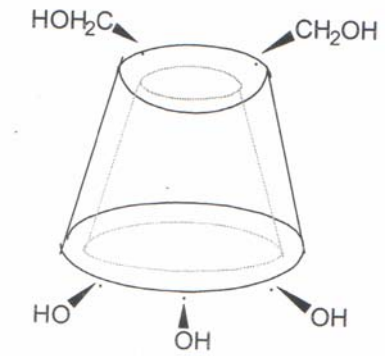
   i. administered orally and is primarily used in tablet and capsule formulations

2. β-cyclodextrin may be used in both wet granulation and direct compression.
3. β-cyclodextrin can be used in Eye drops solutions, Suppositaries, cosmetics.

CYCLODEXTRINS IN MONOMOLECULAR INCLUSION COMPLEXATION

Monomolecular inclusion complexes involve the entrapment of a single in the cavity of one host molecule. Monomolecular host structures are represented by cyclodextrins.

Their ability to form inclusion compounds in aqueous solution is due to the typical arrangement of the glucose units.The molecule actually exists as a



truncated cone. The interior of the cavity is relatively hydrophobic because of the CH_2 groups, where as the cavity entrances are hydrophobic owing to the presence of the primary and secondary hydroxyl groups. β-cyclodextrins are having internal diameter almost $6A^0$.Cyclodextrins are studied as solubilising and stabilizing agents in pharmaceutical dosage form.

Description:

β-cyclodextrins occur as white, practically odourless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

Typical properties of β-cyclodextrins

Compressibility	:	21- 44%
Density (bulk)	:	0.523g/cm^3
Density (tapped)	:	0.754g/cm^3
Melting point	:	255-265^{0}C
Moisture content	:	13.0 – 15.0% w/w
Particle size distribution	:	7.0 – 45.0 µm

Physical characteristics:

Solubility:

Soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20^{0}C, 1 in 20 at 50^{0}C, practically insoluble in acetone, ethanol (95%) and methylene chloride.

Specific rotation : +162.0

Surface tension (at 25^{0}C) : 71 mN/m (71 dynes/cm)

Stability and Storage Conditions

β-cyclodextrin and cyclodextrins are stable in the solid state if protected from humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

Method of manufacture

Cyclodextrins are manufactured by the enzymatic degradation of starch using specialized bacteria. For example, β-cyclodextrin is produced by the action of the enzyme **cyclodextrin glucosyl transferase** upon starch or a starch hydrosylate. An organic solvent was used to direct the reaction that produces β-cyclodextrins and to prevent the growth of micro-organisms during the enzymatic reaction.

Incompatibilities:

The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of Hydroxypropyl-β-cyclodextrins.

2-HYDROXYPROPYL β-CYCLODEXTRIN

CAS number : (98513-20-3)

Appearance : white crystalline powder

Molecular structure:

Synonyms : 2HPβ-CD

Solubility : white crystalline powder

Surface tension : 52-69 mN/m (52-69ynes/cm at 25^0C)

Applications are similar to those for β-cyclodextrin. However it is not nephrotoxic and has been suggested to use in parenteral formulations. The oral and parenteral formulations of HPβ-CD are licensed in Europe and USA. The degree of substitution of hydroxypropyl groups may vary.

Safety of cyclodextrins

Cyclodextrins administered orally is metabolised by microflora in colon, forming the metabolites maltose, maltodextrin and glucose, which are themselves further metabolized before being finally excreted as CO_2 and H_2.

REVIEW OF LITERATURE

Chowdary KPR and Hynavathi R *et.al.,*[18] studied the enhancement of dissolution rate of meloxicam. Solid dispersions of meloxicam in polyvinyl pyrrolidine, hydoxy propyl methyl cellulose, hydroxyl propyl cellulose, polyethylene glycol 6000 and solvent deposited systems on lactose, soluble starch, methyl crystalline cellulose, di calcium phosphate, silica gel and their selected tablet formulations were investigated with an objective of enhancing the dissolution rate of meloxicam. A marked enhancement in the dissolution rate and dissolution rate of meloxicam. A marked enhancement in the dissolution rate and dissolution efficiency of meloxicam was observed with all solid dispersions and solvent deposited systems. Among the carriers used, PVP gave highest enhancement in the dissolution rate of meloxicam at 1:9 ratio of drug and carrier and in case of solvent deposited systems MCC and DCP gave the maximum enhancement of dissolution rate.

Duncan Q.M. Craig *et.al.,*[19] reported the mechanism of drug release from solid dispersions in water soluble polymers. In this review the concusses with regard to the solid structure and dissolution properties of solid dispersion is critically assessed. In particular the theory of carrier and drug controlled dissolution were highlighted. A model is proposed where by the release behaviour from the dispersions may be understood in terms of the dissolution or otherwise of the drug into the concentrated aqueous

polymer layer adjacent to the solid surface, including a derivation of an expansion to describe the release of intact particles from the dispersions.

Nagaraja.P *et.al.,*[20] sensitive spectrophotometric method for the determination of indomethacin in capsules. A single, sensitive and selective spectrophotometric method for the determination of indomethacin (INM) either in pure form or in capsules is described. The method is based on the coupling reaction of hydrolysed INM with diazotized p-phenylenediamine dihydrochloride (PPDD) in sulphuric acid medium o give to give a red coloured product having the absorption maximum at 510 nm. The product is stable for20 hours.

Beer's law is obeyed in the concentration rng of 0.2-10µg/ml. Results of the proposed method compare favourably with those of the official methods and offer the merits of sensitivity and stability. Common excipients used as additives in pharmaceutical preparations do not interfere in the proposed method.

Tirkkonen.S *et.al.,*[21] buffer controlled release of indomethacin from ethylcellulose microcapsules. The rate of release of indomethacin from ethyl cellulose microcapsules prepared from co-acervation was studied using internal buffer, dibasic sodium phosphate (DSP), to increase the solubility of the core. The dissolution rate of the drug was determined in phosphate buffer solutions of varying pH and concentration. The role of the stagnant diffusion layer at the microcapsule surface was also evaluated by changing the mixing in the dissolution test. Indomethacin release was accelerated considerably with increasing amounts of DSP in

the core. DSP increases the pH inside the microcapsules, thus enhancing the release of the acidic drug. Increasing bulk solution pH increased the release rate of indomethacin, the enhancing effect being more pronounced with buffered microcapsules. Neither increasing phosphate concentration of the bulk solution nor increasing mixing of the microcapsules influenced the rate of release of indomethacin from unbuffered capsules. With buffered capsules the increase in phosphate concentration of bulk solution prevented leaching out of internal phosphate increasing in the release rate of indomethacin. The release of indomethacin also accelerated slightly with increasing mixing.

Casella.R et al[22]., solid state β-cyclodextrin complexes containing indomethacin, ammonia and water. In formation studies. Five samples were prepared with β-cyclodextrin and the insoluble , non-steroidal, anti-inflammatory drug indomethacin. The complexes were found to contain the drug , water and ammonia in several unique combinations. It was theorized the complex were tri-molecular in nature and their formation was controlled by a hydrophobic/hydrophilic balance created within the β-cyclodextrin ring cavity prior to complex formation. Each complex was characterized by ultra-violet, infrared, NMR, powder X-ray diffraction, DSC and thermogravimetric techniques. These characterizations revealed distinct differences among the five complexes.

Sanjula Baboota *et.al.,*[23] have studied the formulation of tablet containing inclusion complexes of meloxicam, a non steroidal anti-inflammatory drug (NSAIDs), with betacyclodextrin and 2-hydroxy propyl

betacyclodextrin. Inclusion complexes were prepared by freeze drying method and formed inclusion complexes were evaluated by FT-IR, X-ray diffraction, DSC and scanning electron microscopy. The dissolution studies revealed that all the formulation showed an increased rate and was more in alkaline medium, which may be due to the ionisation of the drug as it is a weak acid. The DSC thermograms of meloxicam displayed its endothermic melting peak at 252^0c indicating the formation of string cyclodextrin-drug complex. The FT-IR spectra indicates possibility of interaction between β-CD/HP-βCD and conversion of meloxicam to amorphous state during freeze drying.

Chowdary K.P.R *et.al.,*[24] has studied the dissolution enhancement of itraconazole by complexation with β- and hydroxypropylβ-cyclodextrin (HPβ-CD). The formation of itraconazole (ITR) with β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HPβ-CD) in aqueous solution and in solid state and the possibility of improving the solubility and dissolution rate of ITR via complexation with the above cyclodextrins were investigated. The phase solubility studies indicated the formation of a 1:1 inclusion complex in solution with both β-CD and HPβ-CD. the apparent stability constant (k_c) was $206.2M^{-1}$ AND $270M^{-1}$ for β-CD and HPβ-CD complexes, respectively. DSC studies indicated the formation of solid inclusion complexes of ITR – β-CD and ITR – HPβ-CD at 1:4 ratio only. Solid complexes of ITR – β-CD and ITR – HPβ-CD (1:1and 1:2 M) prepared by kneading and co-evaporation methods exhibited higher rates of dissolution and dissolution efficiency values than the corresponding

physical mixtures and ITR itself. Higher dissolution rates were observed with kneaded complexes than those prepared by complexation techniques. Increases of 23.4 fold and 83.4 fold in the dissolution rate were observed respectively with ITR – β-CD (1:2M) and ITR – HPβ-CD (1;2 M) kneaded complexes.

Sardar Ameer Ali *et.al.,*[25] has studied the effect of β-CD on piroxicam pharmacokinetics and on *in-vitro* absorption using *in situ* rat gut technique. Complexation of the drug in the gastrointestinal fluid may alter the rate and extent of absorption of the drug. Since the complex formation very well applied in the administration of water soluble complexes of drug; that are incompletely absorbed because of poorly water solubility; the effect of β-CD on piroxicam pharmacokinetics and on *in vitro* absorption was studied. The pharmacokinetics of piroxicam, a potent anti-inflammatory agent and piroxicam in combination with β-CD was studied in 9 healthy human volunteers. The plasma concentration of piroxicam was assayed by UV spectrophotometric method. The relative bioavailability of piroxicam is only 11% on comparing with the formulation containing piroxicam and β-CD in combination. *In vitro* absorption study using *in situ* rat gut technique showed a great rate of transport of piroxicam when combined with β-CD. This increase in bioavailability and rate of transport is due to the formation of inclusion complex by β-CD which in turn increases the solubility.

Nalluri Buchi, Chowdary K.P.R *et.al.,*[26] has studied inclusion complexation and dissolution properties of nimesulide and meloxicam

hydroxypropyl-β-yclodextrin binary systems. The purpose of the work is physicochemical characterisation of nimesulide (NI) meloxicam(ME) – hydroxypropyl-β-cycloextrin (HP-β-CD) binary systems both in solution and solid states and to improve the pharmaceutical properties of NI and ME via inclusion complexation with HP-β-CD. Binary systems of NI and ME with HP-β-CD have been characterised both in solution and solid state by different physicochemical methods. Three types of drug – HP-β-CD binary systems namely physical mixtures (PM), kneaded system (KS) and co-evaporated system (CS) in 1:1 and 1:2 molar ratios were prepared. Phase solubility and H-NMR spectroscopic studies in solution state revealed 1:1 complexation of NI and ME with HPβ-CD. A partial inclusion of NI with HPβ-CD at both molar ratios of kneaded an co-evaporated systems and a true inclusion of ME with HPβ-CD at both molar ratios of co-evaporated systems in solid state was confirmed by differential scanning calorimetry (DSC), powder X-ray diffractometry (powderX-RD) an d scanning electron microscopy (SEM) studies. Dissolution properties of NI and ME-HPβ-CD binary systems were superior when compared to corresponding pure drugs. The aqueous solubility and dissolution properties of NI and ME can be improved by inclusion complexation with HPβ-CD.

Roger A. Rajewski *et.al.,*[27] studied pharmaceutical applications of cyclodextrins-2. *In-vitro* drug delivery. The objective of this review is to summarise and obtain recent findings and applications of both modified and unmodified cyclodextrins for in vivo drug delivery. This review focuses

on the use of cyclodextrins for parenteral, oral, ophthalmic and nasal drug delivery. Other routes including dermal, rectal and pulmonary delivery are also briefly addressed. This primarily focuses on the newer findings concerning cyclodextrin derivative which are likely to receive regulatory acceptance due o improved aqueous solubility and safety profiles as compared to this modified cyclodextrin. Many of the applications reviewed involve the use of hydroxyl propyl β-cyclodextrin (HPβ-CD) and sulfo butyl ether β-cyclodextrin (SBC β-CD), which show promise of reactor safety while maintaining the ability to form inclusion complexes. The advantages and limitations of HPβ-CD and SBC β-CD and another cyclodextrins are addressed.

Juzio Nishijo *et.al.,*[28] **s**tudied inclusion complex of 8-anilino naphthalene-1-sulfonate with β-CD. The interaction of 8-anilinonaphthalene-1 sulfonate with β-CD was investigated in 0.1M phosphate buffer at pH7.4 by fluorescence spectrophotometry. Utilizing the fact that the fluorescence intensity of 8-anilinonaphthalene-1-sulfonate increases in the presence of β-cyclodextrin, the thermodynamic parameters for the inclusion complex formation were determined as follows: Δ^0G = -2.52 Kcal /mol at 25^0C, ΔH^0 = 1.92 Kcal/mol, and ΔS^0 = 2.1 eu. The driving forces for the inclusion complex formation were considered to be vanderwaals-london dispersion force and hydrophobic interaction. Also, for the measurements of ^{1}H-NMR spectra and from studying the corey- pauling-koltun (CPK) model, the structure of the inclusion complex was discussed.

Alison R. Green *et.al.,*[29] studies heptakis (2,6-di-o-methyl) β-cyclodextrin complexation with antitumor agent chlorambucil. The effects of heptakis (2,6-di-o-methyl)- [3-cyclodextrin (DIMEB) and of β-CD on the aqueous solubility and stability of chlorambucil (CHL) have been compared. In the presence o 1.3 X 10^{-3} M DIMEB, there is a greater than 20-fold increase in the stability of chlorambucil at 37^0C, ph 4.13. Aqueous solubility of CHL IS increased more than 40-fold in the presence of 1.74 X 10^{-2}M DIMEB. The solubility was under the conditions where degradation is minimised (3.0^0C, ph 4.13). In the presence of 1.3 X 10^{-3} M β-CDs, there is a four fold increase in the stability, and with1.74 X 10^{-2}M β-CD, there is a three fold increase in the aqueous solubility of CHL under similar conditions. Stability constants of CHL complex with DIMEB were determined kinetically and spectrophotometrically under various experimental conditions assuming 1:1 inclusion complex formation.

Deasy.P.B *et.al.,*[30] use of extrusion-spheronization to develop an improved oral dosage dorm indomethacin. Two new pelletized formulations of indomethacin were developed and compared against pellets from the proprietary product, Indocid-R. Exclusive dissolution testing involving pH-shift and tophographical profiting showed that the new product containing PVP had slightly faster in vitro release than the commercial product, but surprisingly the other new product containing SLS had reduced drug release. The cause of the anomalous result was shown by solubility studies and scanning electron microscopy to be related to the ability of the wetting agent to promote fragmentation of the microcrystalline

cellulose used as spheronization aid into small crystallites, retarding drug release. The two new products had improved specificity compared to the proprietary product when examined by image analysis. However, on in vivo testing in dogs, the new product contaning sodium lauryl sulphate had the highest bioavaibility of the three preparations examined due to its effect as a penetration enhancer.

Daisuke Iohara *et.al.,*[31] preparation of amorphous indomethacin from aqueous 2,6-di-0-methyl-β-cyclodextrin solution. Indomethacin precipitated exclusively in an amorphous form from aqueous 2,6-di-o-methyl-β-cyclodextrin solutions, whereas it precipitated in form of V polymorph from the solutions of the drug alone, parent cyclodextrins and 2-hydroxypropyl-cyclodextrins. The polymorphic transition of the amorphous form to form V crystals in aqueous solution was markedly inhibited by he addition of 2,6-di-0-methyl-β-cyclodextrin, keeping the amorphous state for at least 5 days at 4^0C, where as it quickly transformed to form V crystals in the absence of 2,6-di-o-methyl-β-cyclodextrin, and it suppressed the solution mediated polymorphic transition of amorphous form of indomethacin to form V crystals in aqueous solution. The current results suggested that 2,6-di-o-methyl-β-cyclodextrin is useful for isolation of amorphous indomethacin.

Karneto Uekama *et.al.,*[32] (1992) studied the inhibitory effect of 2-Hydroxy Propyl β-cyclodextrins on crystal growth of Nifedipine during storage. To prevent the crystal growth of Nifedipine during storage 2-Hydroxy Propyl β-cyclodextrin was employed as a hydrophilic drug carrier

and compared polyvinyl Pyrrolidine. Although PVP initially retarded the crystallization of Nifedipine it failed to control the increase of crystal size after prolonged storage.

Suresh and Pradesh[33]., (1999) were studied about the solid dispersion of curcumin. They used the different carrier such as HPMC, HEC, PVP, high molecular weight PEG such as 1500, 4000, 20000, polyaxomars such as cremophor and lutrol-127 for the preparation of solid dispersions. Both fusion and solvent methods were adopted curcumin was successfully solubilised using cremophor and PEG 20000 Release pattern may be first order kinetics.

Nageswara Rao *et.al.,*[34] (2001) studied on maltodextrin-piroxicam solid dispersions. They concluded that the solubility of the piroxicam increased linearly with increase in maltodextrin concentration. From SC results no compatibility problem recognized. An improvement in the dissolution rate of piroxicam in solid dispersions with maltodextrin was demonstrated.

The improvement in the dissolution efficiency of poorly soluble naproxen was demonstrated by Patil et al.,(2001) they prepared the solid dispersions by common solvent method and melting method by using the carriers PEG_{6000} , PEG_{4000} and polyvinyl pyrrolidine. From the dissolution studies the pure only 56.5% was dissolved, but the dissolution of the drug was increased with increase in carrier's ratio in the formulations. They concluded that among the two methods, the melting method was

satisfactory and showed dissolution of drug PEG_{6000} is a suitable carrier for Naproxen to enhance the dissolution rate.

Masataka saito *et.al.,*[35] (2002) prepared the solid dispersions of griscofulvin using saccharides by a new method called roll mixing process. They investigated that the solubility of griseofulvin was higher in mixtures with higher molecular weight carriers such as corn starch and processed starch. The dissolution of griseofulvin was markedly improved by the GF-British gum role mixture. It was suggested that the saccharides with a high molecular weight are useful carriers of solid dispersions.

Chen.Y *et.al.,*[36] (2004) investigated a method of enhancing the bioavailability of ABT-963 using solid dispersion containing pluronic F-68. The dissolution rate and bioavailability of the poorly water soluble compound ABT-963 was substantially increased by solid dispersion. They investigated that the dosing of the dispersion to fasted dogs resulted in a significant oral bioavailability compared to the conventional capsule formulation.

Gopal Rao *et.al.,*[37] (2005) studied the preparation characterization of solid dispersions of naproxen using carriers such as PVP , PEG_{4000} $PEG_{2000,}$ methyl cellulose and β-cyclodextrin. A marked increase in dissolution rate was observed with all solid dispersions. Among the carriers used naproxen β-cyclodextrin gave the highest improvement in dissolution rate.

Natalijazaje *et.al.,*[38] (2005) studied the physical properties and dissolution behaviour of nifedipine with mannitol solid dispersions by hot

melt method. They investigated that the dissolution rate enhancement was attributed to improved wetting of nifedipine crystals due to mannitol particles, Attached on the surface, as inspected by means of scanning electron microscopy.

Guy van den Mooter *et.al.,*[39] (2006) reported an increase in the dissolution rate of itraconazole by solid dispersions prepared with inutec SPI, a new polymeric surfactant by spray drying and hot-stage extrusion. The dissolution properties of the solid dispersions were significantly improved in comparison to pure itraconazole.

Patel and **Patel[40]., (2006)** showed that there is a marked effect on enhancement of dissolution rate of valdecoxib when used as solid dispersion system. They used mannitol, polyethylene glycol4000, and polyvinyl pyrrolidne K-12 as carriers for the preparation of solid dispersions. The tablet formulation containing PVP K_{12} solid dispersions exhibits 100% drug release in 20min.

PURPOSE OF WORK

With the perspective of enhancing the bioavailability of drugs, much attention has been focussed on the problems of drug solubility. So poor solubility or poor wettability may lead to decrease in its bioavailability. The dissolution of the drug from its dosage form is an important parameter in the absorption which is also limiting step.

The dissolution rate can be improved by increasing the surface area by reducing the particle size. There are several methods to reduce the particle size and they are (1) conventional trituration (2) ball milling (3) fluid energy micronization (4) controlled precipitation by change of solvents or temperature (5) application of ultrasonic waves and spray drying (6) Kneading method (7) Co-evaporation method. Although the reduction of size can be easily accomplished, the resultant fine particles may not produce the expected faster dissolution and absorption. This primarily results from possible aggregation and agglomeration of the fine particles due to their increased surface free energy and subsequent strong vanderwaal's attraction between non-polar molecules.

The present studies are aimed for overcoming these common problems by introducing solid dispersion technology using various carriers and thus improve its dissolution characteristics. This study deals with an

effective anti-inflammatory drug. Indomethacin which is poorly soluble in water where the dissolution rate is limited.

The work was carried out according to the following steps:

1. Literature survey on solid dispersions, methods and carriers for solid dispersion and for indomethacin.
2. Preparation and Evaluation of Solid dispersions o indomethacin with β-CD and HPβ-CD.

ANALYTICAL METHODS

Indomethacin can be analysed by the following methods

They are:

Phosphorimetric determination of Indomethacin in pharmaceutical formulations[45].

Spectroflourimetric, HPLC[46] and colorimetric estimation in biological samples.

Method used in this study

Potassium dihydrogen phosphate, 0.2M solution

Accurately weight 27.318 gm of potassium dihydrogen phosphate is dissolved in 1000 ml of distilled water.

Sodium hydroxide 0.2N solution

Accurately weigh 8 gm of sodium hydroxide and dissolved in 1000ml of distilled water.

Preparation of pH 7 phosphate buffer

Place 50 ml of the 0.2M potassium dihydrogen phosphate in a standard volumetric flask. Add 29.1 ml of 0.2M sodium hydroxide solution to the flask and make up the volume with distilled water.

Preparation of pH7.2 phosphate buffer

Place 50 ml of potassium dihydrogen phosphate in a 200 ml standard volumetric flask. Add 4.7 ml of sodium hydroxide solution to this flask and make up the volume with distilled water.

Procedure for standard graph preparation

Accurately weigh 100 mg of indomethacin and transfer to a 100 ml volumetric flask. Add minimum quantity of methanol to get a clear solution. Then add phosphate buffer pH7.0 to make up the volume to 1000 μg/ml. This gives stock solution.

From this solution pipette out 1 ml and make up the volume to 10 ml with phosphate buffer pH7.0. This solution contains 100 μg/ml.

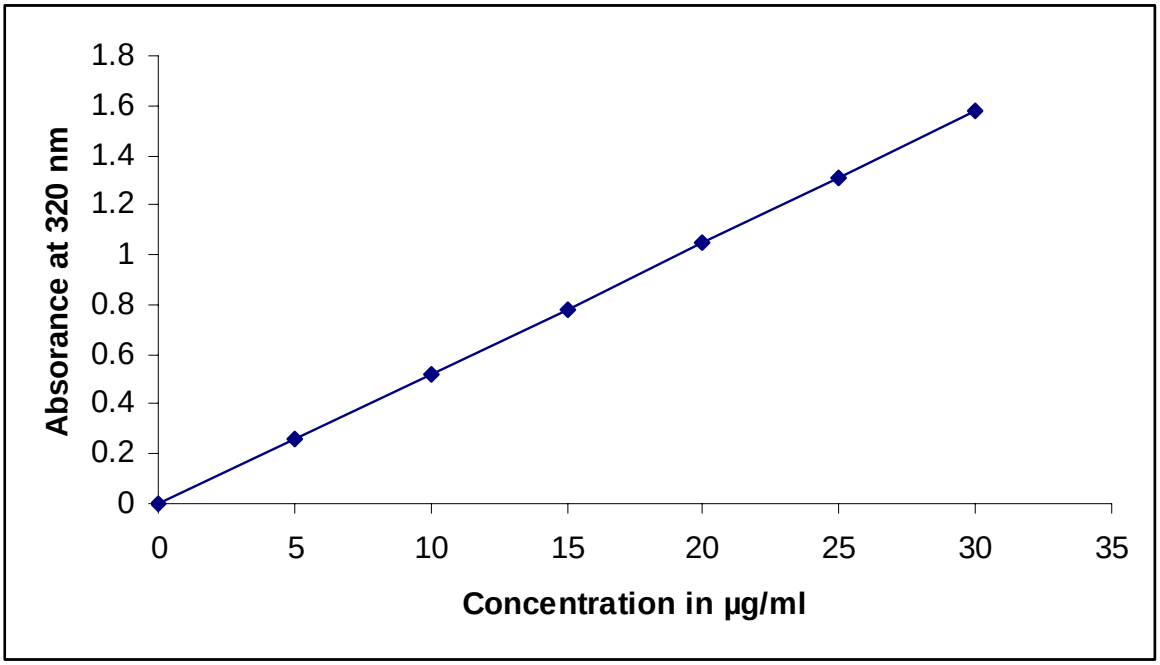
From above solution pipette out 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, 3 ml into five separate test tubes and then make up the volume to 10 ml to give 5, 10, 15, 20, 25 and 30 μg/ml concentrated solution. A blank was also prepared with out drug. The absorbance was measured at 320 nm.

The results are shown in the below table no 2 and figure no.2 follows:

Table no : 2 ABSORBANCE OF INDOMETHACIN

Sl.No	Concentration in µg/ml	Absorbance at 320 nm
1	5	0.26
2	10	0.521
3	15	0.779
4	20	1.049
5	25	1.306
6	30	1.578

Figure no : 2 STANDARD GRAPH OF INDOMETHACIN



PREPARATION AND EVALUATION OF INDOMETHACIN SOLID DISPERSIONS

Materials and equipment used

Indomethacin	-	Max India Limited, Mysore.
β-cyclodextrin	-	Burgoyner Burbidges and Co.. Mumbai.
Hydroxypropyl-β-cyclodextrin	-	Burgoyner Burbidges and Co.. Mumbai
Methanol	-	Fischer Inorganics, Chennai
.Chloroform	-	Fischer Inorganics, Chennai
Vacuum pump	-	Gelman Sciences.
Magnetic Stirrer	-	SR No GEMS 1708 Demi Stirrer Equipment, Mumbai.
Dissolution Apparatus	-	Electro Lab TDT-08L
UV/Vis. Spectrophotometer	-	JASCO V-530
Analytical Balance	-	Dhona 200D.

SOLID DISPERSIONS OF INDOMETHACIN

Solid dispersions technology can be used to improve the *in-vitro* and *in-vivo* dissolution properties of poorly water soluble drugs. Indomethacin is practically insoluble in water; the dissolution rate from solid dispersion was effected by carrier concentration. β-cyclodextrin and

hydroxypropyl-β-cyclodextrins at drug:carrier ratios of 1:1, 1:3, 1:9 were prepared using kneading and co-evaporation methods.

PROCEDURE FOR PREPARATION OF SOLID DISPERSIONS OF INDOMETHACIN BY CO-EVAPORATION METHOD

Methanol was used as a solvent. The aqueous solution of cyclodextrin was added to the solution of indomethacin methanol. The resulting mixture was stirred for one hour and evaporated at a temperature of 55^0C in the hot air oven until dry. The dried mass was pulverised and sieved through mesh no 100.

PROCEDURE FOR PREPARATION OF SOLID DISPERSION OF INDOMETHACIN BY KNEADING METHOD

The solvent blend of methanol and water is used here. Indomethacin and cyclodextrin were triturated in mortar with small volume of solvent blend of water-methanol. The thick slurry was kneaded for 45 min and then dried at 55^0C in the hot air oven till it gets dried. The dried mass was pulverised and sieved through 100 mesh.

Table no : 3 DRUG CARRIER RATIOS AND RESPECTIVE AMOUNTS TAKEN FOR SOLID DISPERSION

Drug carrier ratio	Drug (mg)	Carrier (mg)
1:1	1000	1000
1:3	500	1500
1:9	200	1800

CHARACTERISATION OF INDOMETHACIN SOLID DISPERSION

- Thin layer chromatography
- IR spectral analysis
- X-ray diffraction studies
- Differential scanning calorimetry

EVALUATION OF INDOMETHACIN SOLID DISPERSION

- Drug content uniformity
- In-vitro dissolution studies

THIN LAYER CHROMATOGRAPHY

A thin layer chromatographic method was carried out to study the interaction between the drug and the carrier and also to confirm the chemical stability of the solid dispersions prepared. For this, pure indomethacin and the solid dispersions prepared with various carriers by solvent evaporation method and kneading method at 50:50 ratios were subjected to chromatographic studies. Which are shown in table no.4.

The TLC system used for the study is given below

Precoated TLC plates : manufactured by SD fine Chemicals ltd, Mumbai.

Absorbent layer	:	Silica gel GF 254
Layer thickness	:	250 µm
Size	:	10 X 20 cm
Separation technique	:	Ascending
Chamber saturation	:	The chamber was lined on three sides with filter paper and saturated for 45 min.

Mobile phase	:	Mixture of 70 volumes of ether and 30 volumes of light petroleum
Preparation of sample	:	Suitable quantity of the sample was dissolved in methanol and spotted.
Amount applied	:	10 µL
Detection	:	Iodine chamber

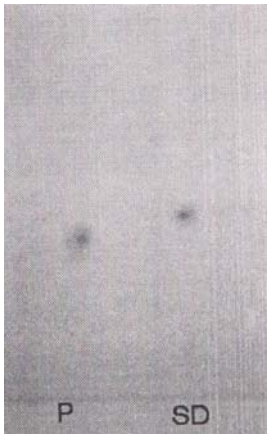
.

Table no : 4 Rf VALUES OF DRUG AND COMBINATION WITH POLYMERS

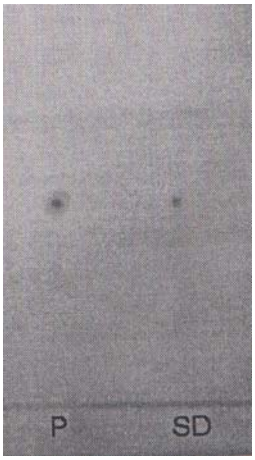
Sample	Rf value	Number of spots
Pure drug	0.4886	Single
INM:β-CD (Co-evaporation)	0.4892	Single
INM : β-CD (Kneading)	0.4962	Single
INM:HPβ-CD (Co-evaporation)	0.4914	Single
INM:HP β-CD (Kneading)	0.4862	Single
INM : Mixture of polymers(Kneading)	0.4722	Single
INM : β-CD (Physical mixture)	0.4882	Single
INM : HP β-CD (Physical mixture)	0.4916	Single

Figure no.3. TLC OF INDOMETHACIN AND SOLID DISPERSIONS WITH β-CD AND HPβ-CD AND COMBINATION OF β-CD AND HPβ-CD.

P= Pure drug of INM
SD= Solid Dispersion of
INM : HPβ-CD (1:1)



P= Pure drug of INM
SD= Solid Dispersion of
of INM : β-CD (1:1)



P = Pure drug of INM
SD = Solid Dispersion
INM : β-CD & HPβ-CD(1:1)

FT-IR SPECTRAL ANALYSIS

Using Fourier Transform Infra Red (FTIR) spectrometer compatibility studies of both drug and solid dispersions were carried out. The IR spectra obtained is given in figure 4 to 8. It was observed that the IR spectra for pure indomethacin were matching with that of indomethacin reference standard spectrum.

The spectra obtained from solid dispersions matched with the original spectra. Hence there was no appearance or disappearance of any characteristic peaks, which confirmed the absence of chemical interaction between the drug and the carriers used. .

POWDER X-RAY DIFFRACTOMETRY

The powder X-Ray Diffraction patterns were recorded using a Siemens Kristallofex D-5000 diffractometer (Siemen, Munich, Germany)with Cu as anode material and crystal graphite monochromator operated at a voltage of 40 Kv and a current of 30mA. The samples were analysed in the 2θ angle range of 2º to 65º and the process parameters. Which are shown in figure no.9 to 12.

DIFFERENTIAL SCANNING CALORIMETRY

The DSC measurements were performed using mettler- Toledo DSC module controlled by STARe software (Mettler-Toledo GmBH Switzerland). All accurately weighed samples (1 mg of Indomethacin or its equivalents) were placed in sealed aluminium pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of $10^0 C min^{-1}$, over the

temperature range of 30^0C – 220^0C. An empty aluminium pan was used as reference. The figures are shown 13-17.

DRUG CONTENT UNIFORMITY

The Indomethacin solid dispersion which was prepared was tested for the drug content uniformity. From each batch of solid dispersion prepared in different ratios, 100 mg of Indomethacin solid dispersions were taken and analyzed for drug content uniformity. Which are shown in table no.5.

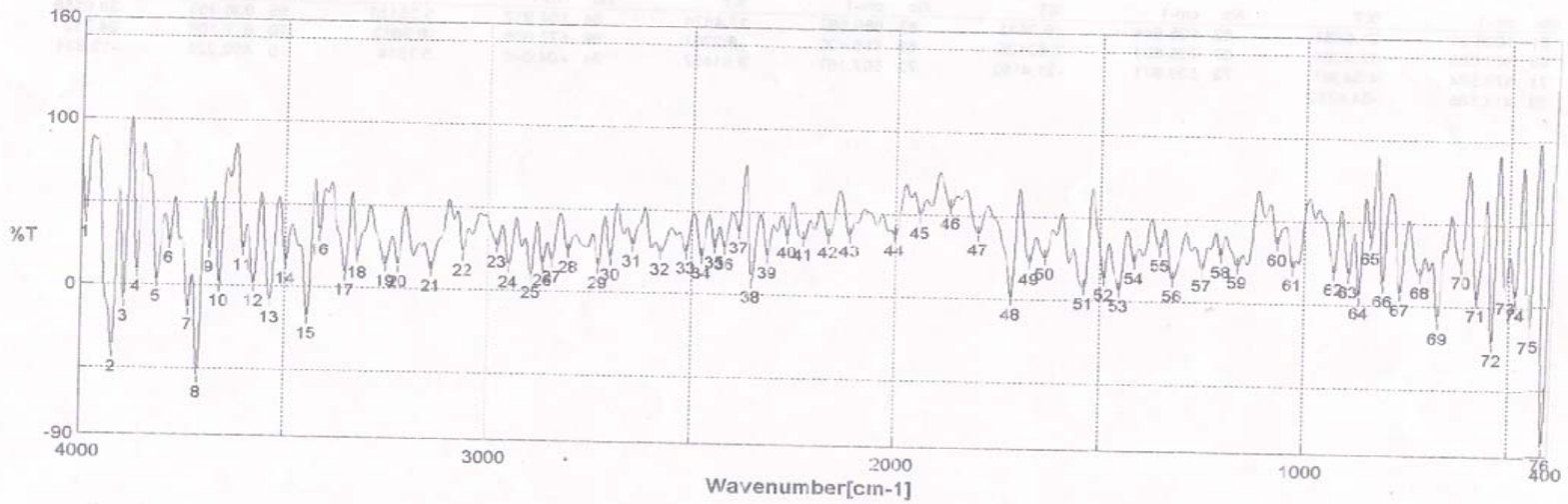
Estimation of Indomethacin In Solid Dispersion By UV Spectroscopy

Accurately weighed amount of SD was dissolved in 100 ml of o.1M pH 7.2 buffer phosphate buffer in a 100 ml volumetric flask which was previously cleaned and dried. The is solution after suitable dilution was measured for absorption at 320 nm in a JASCO V-530 UV-Visible spectrophotometer. The results are shown below.

Table no : 5 DRUG CONTENT UNIFORMITY

Solid dispersions	Drug: carrier	Amount of SD Taken	Expected amount of indomethacin in SD (mg)	%of indomethacin estimated by UV spectrophotometer
Indomethacin β CD (co-evaporation)	1:1 1:3 1:9	200.00 400.00 1000.00	100 100 100	96.2 98.2 99.6
Indomethacin β CD (KM)	1:1 1:3 1:9	200.00 400.00 1000.00	100 100 100	93.2 94.6 98.4
Indomethacin HP β CD (co-evaporation)	1:1 1:3 1:9	200.00 400.00 1000.00	100 100 100	97.4 98.6 99.8
Indomethacin HP β CD (KM)	1:1 1:3 1:9	200.00 400.00 1000.00	100 100 100	97.4 98.4 99.8

Figure no.4. FT - IR SPECTRA OF INDOMETHACIN

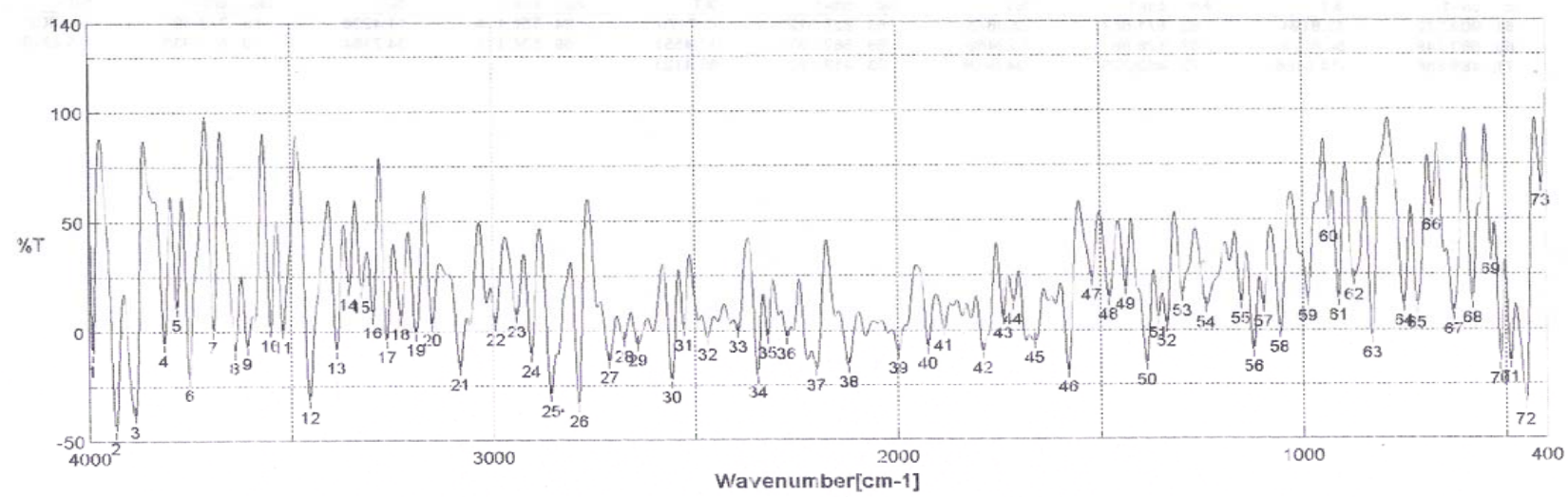


Accumulation	40
Zero Filling	ON
Gain	256
Date/Time	11/27/2008 3:03PM
Operator	C.Geetha
File Name	Pure drug
Sample Name	Pure drug
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	12/4/2008 3:22PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3990	41.1468	2	3923.47	-39.7003	3	3894.54	-8.93225	4	3862.72	8.76002	5	3814.51	2.96966
6	3782.69	25.7735	7	3735.44	-13.6234	8	3711.33	-54.2568	9	3683.37	20.9044	10	3659.27	0.433391
11	3602.38	22.1245	12	3575.38	1.14473	13	3535.84	-8.5479	14	3498.24	15.0076	15	3445.21	-17.6831
16	3415.31	32.3144	17	3351.68	8.53616	18	3320.82	18.9441	19	3253.32	14.2803	20	3221.5	14.1768
21	3140.51	11.7118	22	3061.44	21.3582	23	2977.55	26.8226	24	2948.63	14.6797	25	2894.63	8.95134
26	2866.67	16.1486	27	2843.52	18.4499	28	2803.99	24.4779	29	2729.74	15.4091	30	2700.82	20.411
31	2645.86	28.8723	32	2577.4	24.0567	33	2514.72	24.8885	34	2476.15	22.1692	35	2445.3	28.6354
36	2421.19	27.8155	37	2385.51	38.1197	38	2353.69	8.19866	39	2315.12	23.1896	40	2266.91	35.5763
41	2225.45	34.2392	42	2164.7	36.1239	43	2112.64	36.851	44	2002.71	37.9925	45	1941	49.2217
46	1865.79	54.9502	47	1797.33	39.6142	48	1716.34	1.2479	49	1671.98	22.1313	50	1634.38	25.5121
51	1538.92	8.06636	52	1490.7	13.3901	53	1452.14	7.05881	54	1415.49	23.6238	55	1351.86	31.6009
56	1320.04	13.6227	57	1248.68	19.8915	58	1203.36	28.1505	59	1162.87	22.1852	60	1065.48	36.2223

Figure no.5. FT - IR SPECTRA OF INDOMETHACIN : β-CD IN THE RATIO OF 1:1 (CO-EVAPORATION METHOD)

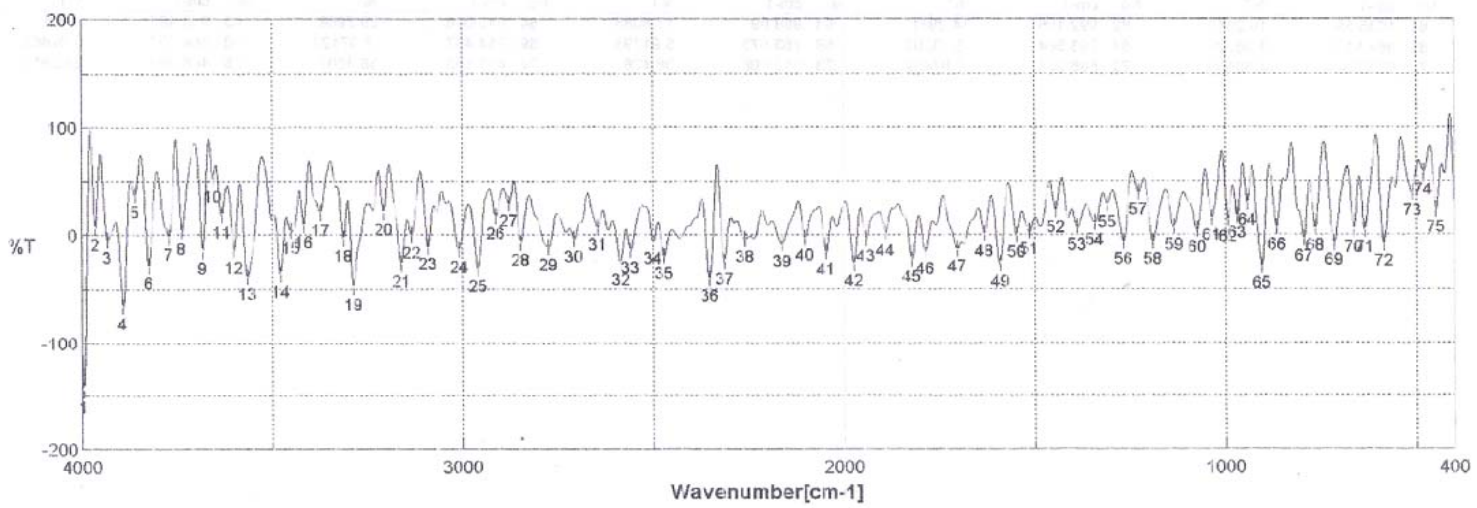


Accumulation	40
Zero Filling	ON
Gain	256
Date/Time	11/27/2008 2:45PM
Operator	C.Geetha
File Name	BC 1
Sample Name	BC 1
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	12/4/2008 2:28PM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3990.96	-10.4191	2	3935.04	-45.329	3	3886.83	-38.1353	4	3814.51	-5.64238	5	3781.72	10.8208
6	3750.87	-21.6815	7	3690.12	0.220135	8	3637.09	-9.15218	9	3607.2	-7.10826	10	3550.31	0.779908
11	3520.42	0.28248	12	3454.85	-31.6979	13	3387.35	-9.33094	14	3355.53	19.8554	15	3324.68	18.9894
16	3295.75	6.9049	17	3262	-4.21147	18	3227.29	6.03908	19	3190.65	-1.1185	20	3150.15	3.49755
21	3082.65	-16.9258	22	2993.94	3.45804	23	2940.91	7.28149	24	2905.24	-11.0747	25	2857.02	-29.1537
26	2788.56	-33.8922	27	2712.39	-13.8349	28	2675.75	-4.19634	29	2642.96	-6.10745	30	2558.11	-22.8274
31	2528.22	0.727118	32	2470.37	-3.47271	33	2394.19	-0.298317	34	2346.94	-20.8053	35	2321.87	-2.81683
36	2274.63	-3.12029	37	2201.34	-17.7177	38	2121.31	-16.3309	39	1958.86	-10.1354	40	1925.57	-7.68646
41	1885.08	0.139844	42	1788.65	-9.84474	43	1738.51	5.87732	44	1712.48	12.6796	45	1661.37	-5.38891
46	1578.45	-18.854	47	1520.6	23.4867	48	1478.17	14.64	49	1437.67	19.1179	50	1384.64	-15.633
51	1354.75	5.67773	52	1334.5	1.86375	53	1295.93	15.9663	54	1237.11	10.6823	55	1152.26	12.3739
56	1121.4	-9.441	57	1096.33	11.0032	58	1055.84	-0.938029	59	986.411	13.4245	60	933.378	49.498

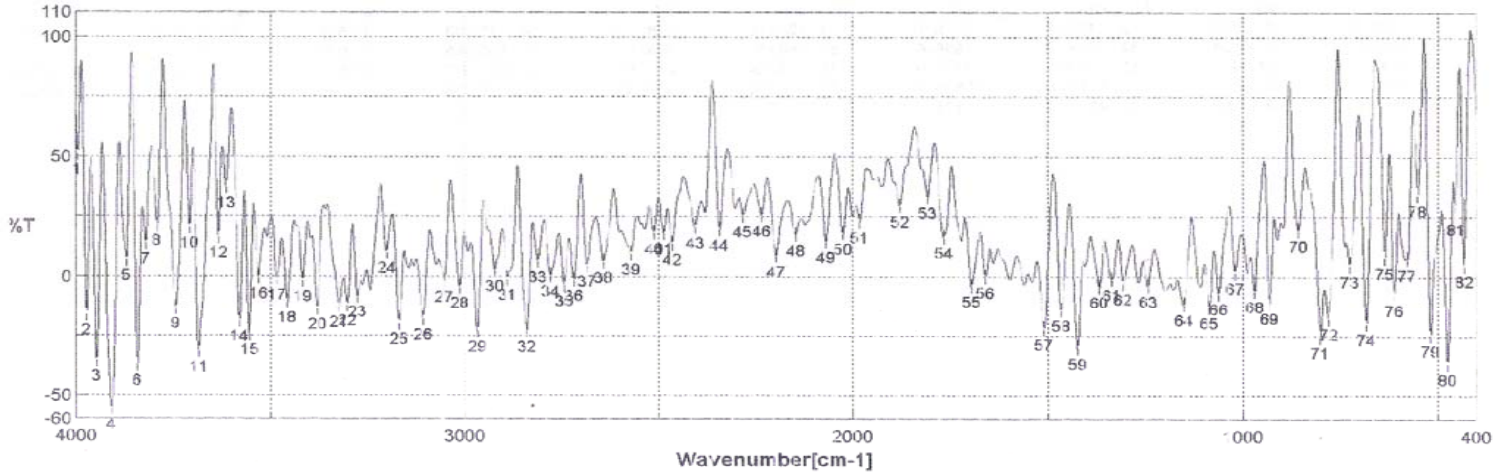
Figure no.6. FT – IR SPECTRA OF INDOMETHACIN : β-CD IN THE RATIO OF 1:1 (KNEADING METHOD)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	256	Scanning Speed	2 mm/sec
Date/Time	11/27/2008 2:52PM	Update	12/4/2008 2:43PM
Operator	C.Geetha		
File Name	BK 1		
Sample Name	BK 1		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3995.78	-144.245	2	3963.96	6.66107	3	3933.11	-5.11337	4	3892.61	-66.1742	5	3860.79	37.0249
6	3824.15	-28.7737	7	3771.12	-1.51932	8	3737.37	3.02781	9	3682.41	-14.9156	10	3655.41	51.6341
11	3632.27	17.7335	12	3599.48	-14.1411	13	3563.81	-38.8672	14	3478.95	-36.2527	15	3450.99	4.38693
16	3418.21	9.21549	17	3374.82	20.5441	18	3314.07	-3.09435	19	3287.07	-48.5869	20	3207.04	20.9068
21	3160.76	-27.0753	22	3133.76	-0.427667	23	3091.33	-10.7919	24	3010.34	-13.8688	25	2960.2	-31.2751
26	2912.95	17.294	27	2878.24	29.2939	28	2846.42	-6.69137	29	2773.14	-11.2515	30	2706.6	-4.03148
31	2644.89	7.013	32	2586.07	-25.3098	33	2560.04	-14.3815	34	2500.26	-5.8064	35	2471.33	-19.6381
36	2351.77	-40.0752	37	2313.2	-25.0839	38	2259.2	-4.25898	39	2161.81	-8.33162	40	2101.06	-2.85923
41	2045.14	-15.6971	42	1972.82	-26.1043	43	1941	-3.58735	44	1889.9	2.03734	45	1820.47	-22.6231
46	1784.8	-15.2496	47	1700.91	-12.5812	48	1629.55	1.35659	49	1569.06	-26.7306	50	1546.63	0.588924
51	1512.88	3.12584	52	1444.42	23.367	53	1387.53	6.82145	54	1341.25	11.6708	55	1308.46	28.0235
56	1266.04	-6.24673	57	1225.54	39.4789	58	1188.9	-6.42761	59	1133.94	7.1812	60	1073.19	4.5511

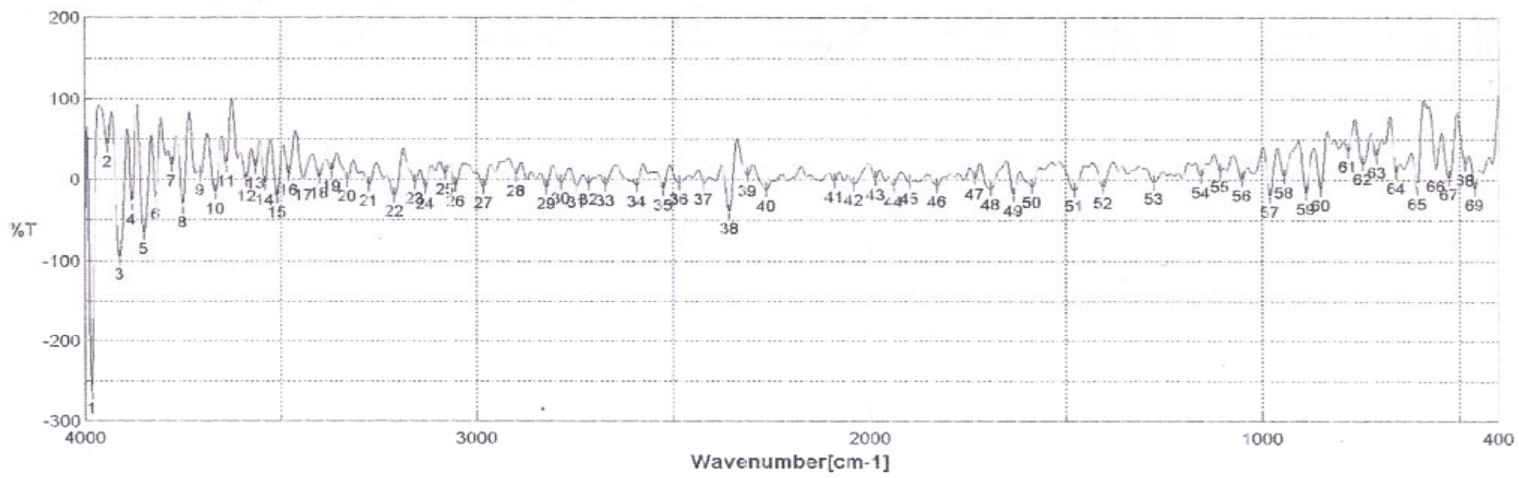
Figure no.7 FT - IR SPECTRA OF INDOMETHACIN : HPβ-CD IN THE RATIO OF 1:1 (CO-EVAPORATION METHOD)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	256	Scanning Speed	2 mm/sec
Date/Time	11/27/2008 2:31PM	Update	12/4/2008 3:12PM
Operator	C.Geetha		
File Name	HP 1		
Sample Name	HP1		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3994.82	51.1279	2	3972.64	-16.1096	3	3947.57	-35.0924	4	3909	-55.3222	5	3871.4	7.22017
6	3842.47	-37.1401	7	3820.29	14.1565	8	3791.37	21.8063	9	3744.12	-13.1555	10	3708.44	20.7156
11	3684.34	-31.2736	12	3633.23	16.8604	13	3613.95	37.285	14	3579.23	-18.4179	15	3554.16	-24.2836
16	3531.02	-0.375554	17	3484.74	-1.04442	18	3457.74	-10.8086	19	3419.17	-1.42049	20	3380.6	-13.4188
21	3324.68	-12.4211	22	3302.5	-11.8909	23	3276.47	-8.22326	24	3200.29	10.4001	25	3166.47	-19.6856
26	3107.72	-17.969	27	3052.76	-1.78504	28	3014.19	-4.40459	29	2967.91	-22.9581	30	2923.56	2.97375
31	2889.81	-0.806272	32	2838.7	-23.0692	33	2810.74	6.49037	34	2777.96	0.713339	35	2742.28	-3.33414
36	2717.21	-1.31986	37	2684.43	4.70667	38	2642.96	6.42878	39	2571.61	9.89801	40	2512.79	18.3169
41	2487.72	18.2506	42	2465.54	13.8625	43	2406.73	20.896	44	2343.09	19.8911	45	2283.3	25.4709
46	2236.06	25.6859	47	2198.45	8.72497	48	2147.35	17.6775	49	2070.21	14.7368	50	2024.89	18.181
51	1982.46	23.0163	52	1880.26	29.6648	53	1807.94	33.2104	54	1766.48	16.5451	55	1696.09	-3.85835
56	1659.45	0.135381	57	1509.03	-21.9096	58	1465.63	-14.2044	59	1424.17	-30.3047	60	1368.25	-4.22333

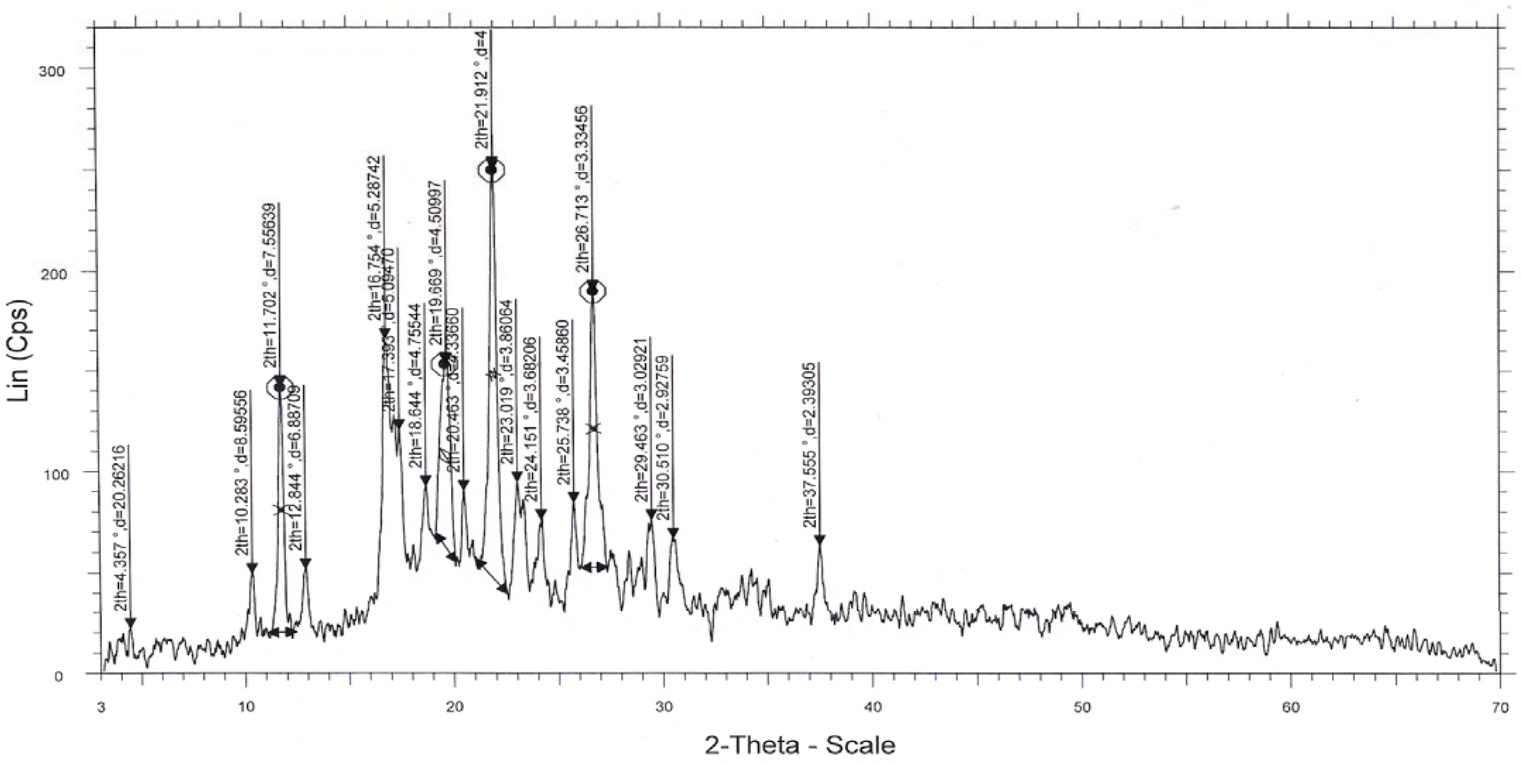
Figure no.8. FT - IR SPECTRA OF INDOMETHACIN : HPβ-CD IN THE RATIO OF 1:1 (KNEADING METHOD)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	256	Scanning Speed	2 mm/sec
Date/Time	11/27/2008 2:50PM	Update	12/4/2008 3:04PM
Operator	C.Geetha		
File Name	HK 1		
Sample Name	HK 1		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3983.25	-263.739	2	3942.75	41.9627	3	3911.9	-96.4847	4	3880.08	-29.488	5	3848.26	-64.8857
6	3818.36	-22.6454	7	3777.87	17.7414	8	3748.94	-32.7782	9	3703.62	6.84827	10	3666.98	-16.0116
11	3639.02	18.2776	12	3587.91	-0.681689	13	3564.77	14.9689	14	3540.67	-5.21196	15	3509.81	-20.8846
16	3479.92	6.81591	17	3443.28	0.0137767	18	3402.78	3.30914	19	3371.92	11.7941	20	3330.46	-0.638329
21	3275.5	-6.04315	22	3210.9	-19.2274	23	3157.86	-3.0344	24	3130.87	-10.0939	25	3080.73	7.55262
26	3054.69	-7.24929	27	2983.34	-9.31947	28	2901.38	6.19044	29	2823.28	-9.46785	30	2785.67	-3.69245
31	2745.17	-8.27545	32	2714.32	-4.57171	33	2670.93	-5.92716	34	2591.86	-7.0995	35	2526.29	-11.2562
36	2484.83	-4.43536	37	2422.15	-4.29503	38	2356.59	-39.905	39	2309.34	5.65819	40	2262.09	-12.4903
41	2088.53	-1.13039	42	2039.35	-5.53354	43	1984.39	1.74568	44	1937.15	-6.99919	45	1896.65	-3.28139
46	1825.29	-7.427	47	1729.83	1.87506	48	1690.3	-10.6948	49	1632.45	-18.5374	50	1585.2	-8.27025
51	1478.17	-12.2176	52	1403.92	-8.63435	53	1275.68	-3.0342	54	1156.12	4.42843	55	1105.98	11.0843
56	1051.01	0.714225	57	979.661	-19.5061	58	943.985	4.31563	59	886.059	-16.1895	60	851.418	-11.9577

Figure no.9. X-RAY DIFFRACTION STUDIES OF INDOMETHACIN SOLID DISPERSION WITH HPβ-CD 1: 1 (KNEADING METHOD)

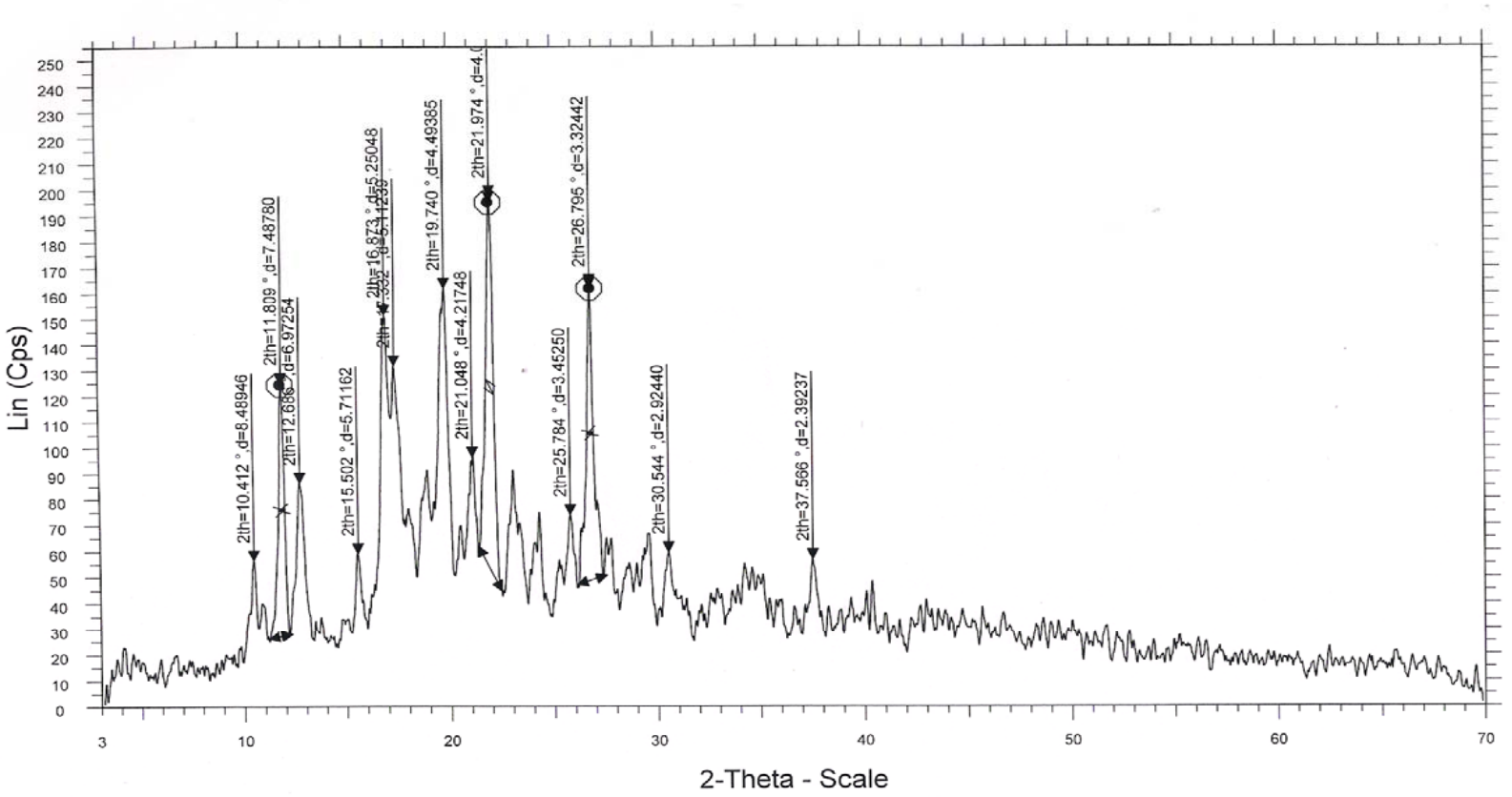


File: SAIFXR081117B-02(HK).raw - Step: 0.010 ° - Step time: 0.2 s - Temp.: 25 °C (Room) - WL1: 1.5406 - kA2 Ratio: 0.5 - Generator kV: 40 kV - Generator mA: 35 mA - Slit Meas.=

1) HK - Left Angle: 20.990 ° - Right Angle: 22.510 ° - FWHM: 0.361 ° - Raw Area: 159.6 Cps x deg. - Net Area: 86.99 Cps x deg.
2) HK - Left Angle: 10.980 ° - Right Angle: 12.380 ° - FWHM: 0.281 ° - Raw Area: 66.05 Cps x deg. - Net Area: 38.81 Cps x deg.
3) HK - Left Angle: 26.030 ° - Right Angle: 27.360 ° - FWHM: 0.332 ° - Raw Area: 130.4 Cps x deg. - Net Area: 61.16 Cps x deg.
4) HK - Left Angle: 19.110 ° - Right Angle: 20.080 ° - FWHM: 0.564 ° - Raw Area: 110.2 Cps x deg. - Net Area: 50.33 Cps x deg.

Operations: Smooth 0.034 | Smooth 0.150 | Background 0.000,1.000 | Import

Figure no.10 X-RAY DIFFRACTION STUDIES OF INDOMETHACIN SOLID DISPERSION WITH HPβ-CD AND β-CD 1:1 (KNEADING METHOD)



File: SAIFXR081117B-03(CK).raw - Step: 0.010 ° - Step time: 0.2 s - Temp.: 25 °C (Room) - WL1: 1.5406 - kA2 Ratio: 0.5 - Generator kV: 40 kV - Generator mA: 30 mA - Slit Meas.=

1) CK - Left Angle: 11.100 ° - Right Angle: 12.250 ° - FWHM: 0.305 ° - Raw Area: 65.12 Cps x deg. - Net Area: 34.71 Cps x deg.
2) CK - Left Angle: 21.290 ° - Right Angle: 22.440 ° - FWHM: 0.395 ° - Raw Area: 124.4 Cps x deg. - Net Area: 63.66 Cps x deg.
3) CK - Left Angle: 26.080 ° - Right Angle: 27.540 ° - FWHM: 0.313 ° - Raw Area: 120.9 Cps x deg. - Net Area: 50.18 Cps x deg.

Operations: Smooth 0.046 | Smooth 0.150 | Background 0.000,1.000 | Import

Figure no.11. X-RAY DIFFRACTION STUDIES OF INDOMETHACIN SOLID DISPERSION WITH β-CD 1:1 (KNEADING METHOD)

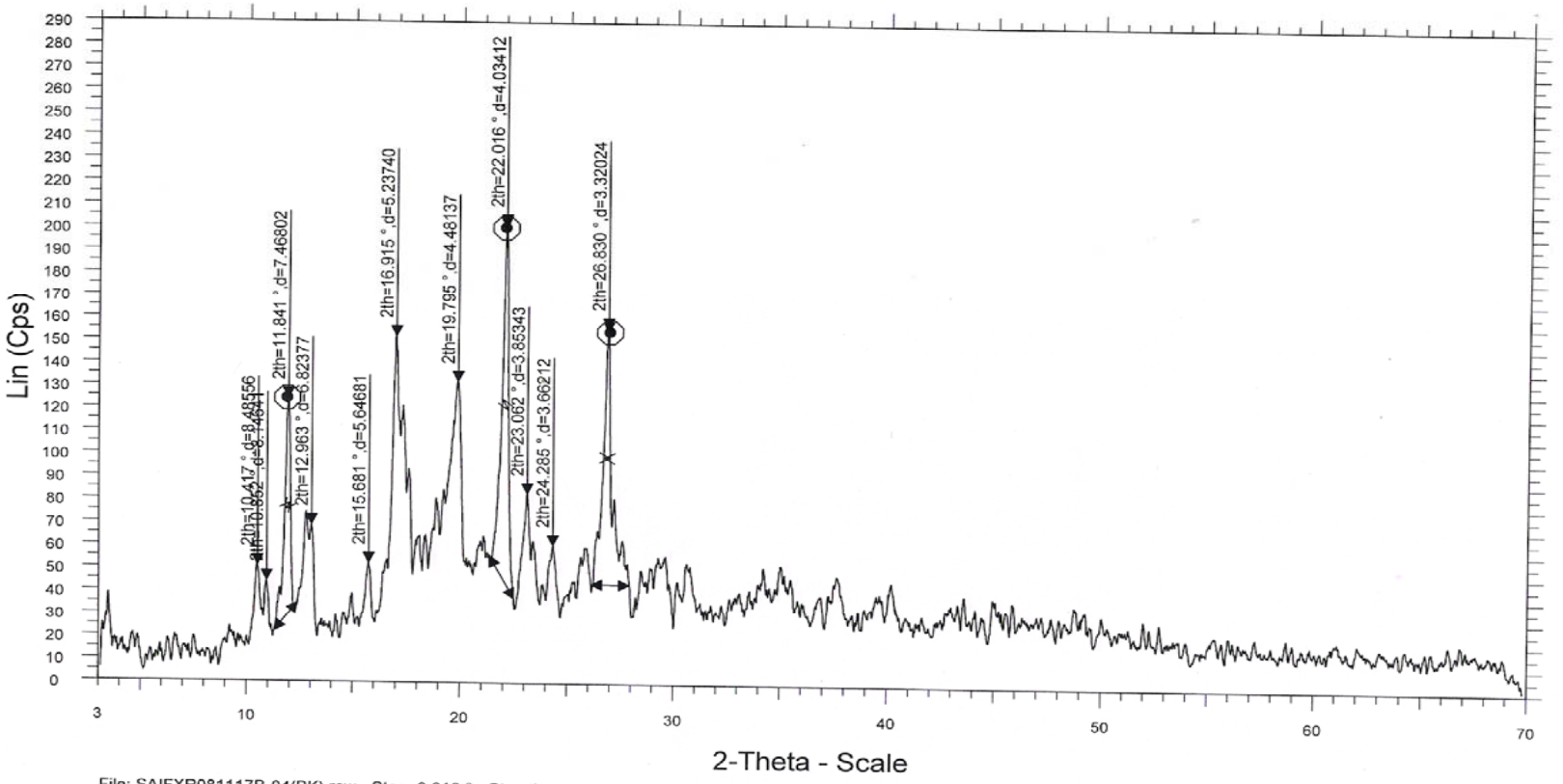
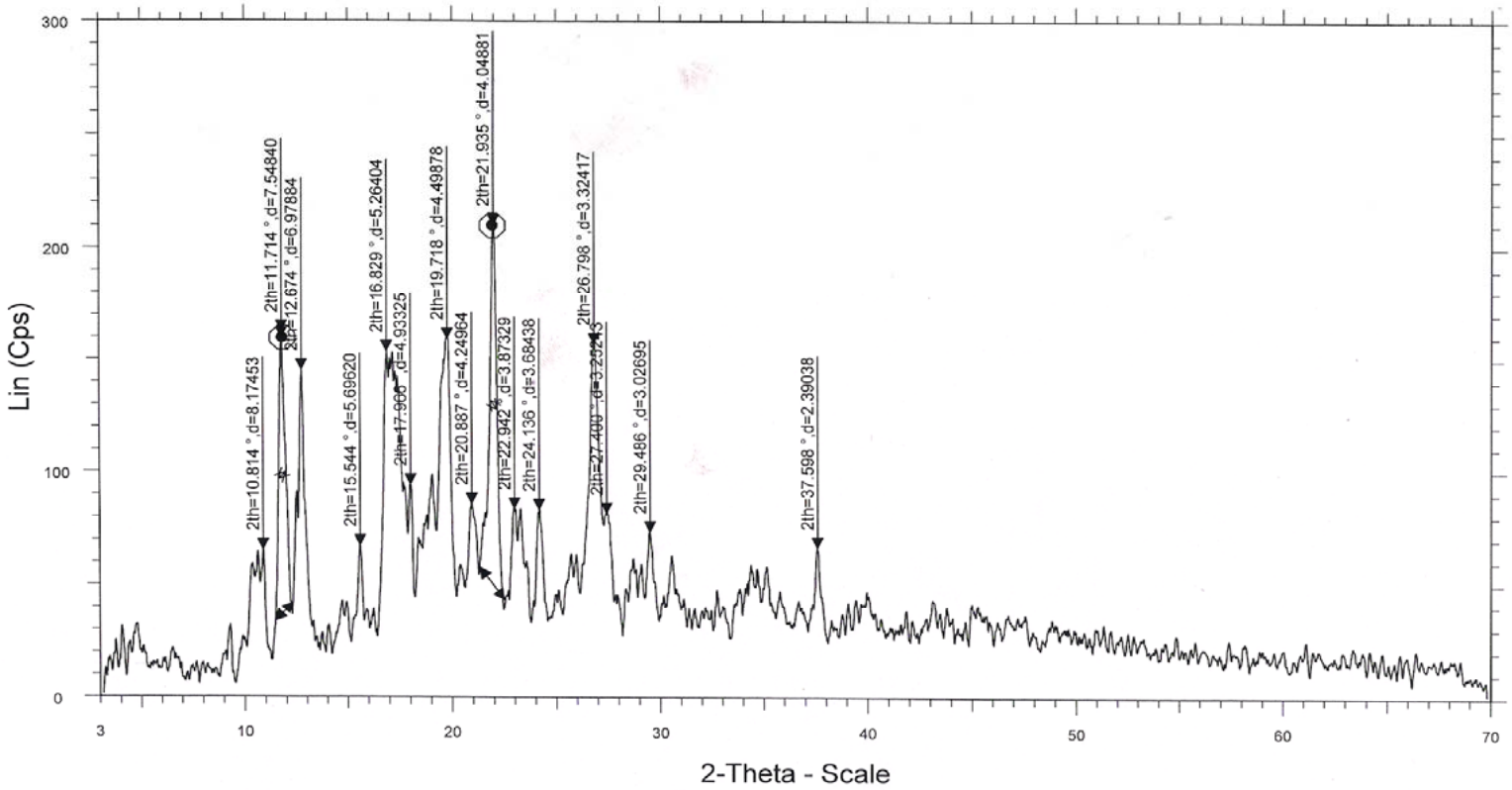


Figure no.12. X-RAY DIFFRACTION STUDIES OF INDOMETHACIN SOLID DISPERSION WITH β-CD 1:1 (CO-EVAPORATION METHOD)



File: SAIFXR081117B-05(BC).raw - Step: 0.010 ° - Step time: 0.2 s - Temp.: 25 °C (Room) - WL1: 1.5406 - kA2 Ratio: 0.5 - Generator kV: 40 kV - Generator mA: 30 mA - Slit Meas.=

1) BC - Left Angle: 21.290 ° - Right Angle: 22.440 ° - FWHM: 0.357 ° - Raw Area: 124.1 Cps x deg. - Net Area: 66.68 Cps x deg.

2) BC - Left Angle: 11.400 ° - Right Angle: 12.250 ° - FWHM: 0.359 ° - Raw Area: 76.14 Cps x deg. - Net Area: 44.65 Cps x deg.

Operations: Smooth 0.028 | Smooth 0.150 | Background 0.000,1.000 | Import

Figure No.13. DSC STUDIES OF INDOMETHACIN SOLID DISPERSION WITH HPβ-CD 1:1 (CO-EVAPORATION METHOD)

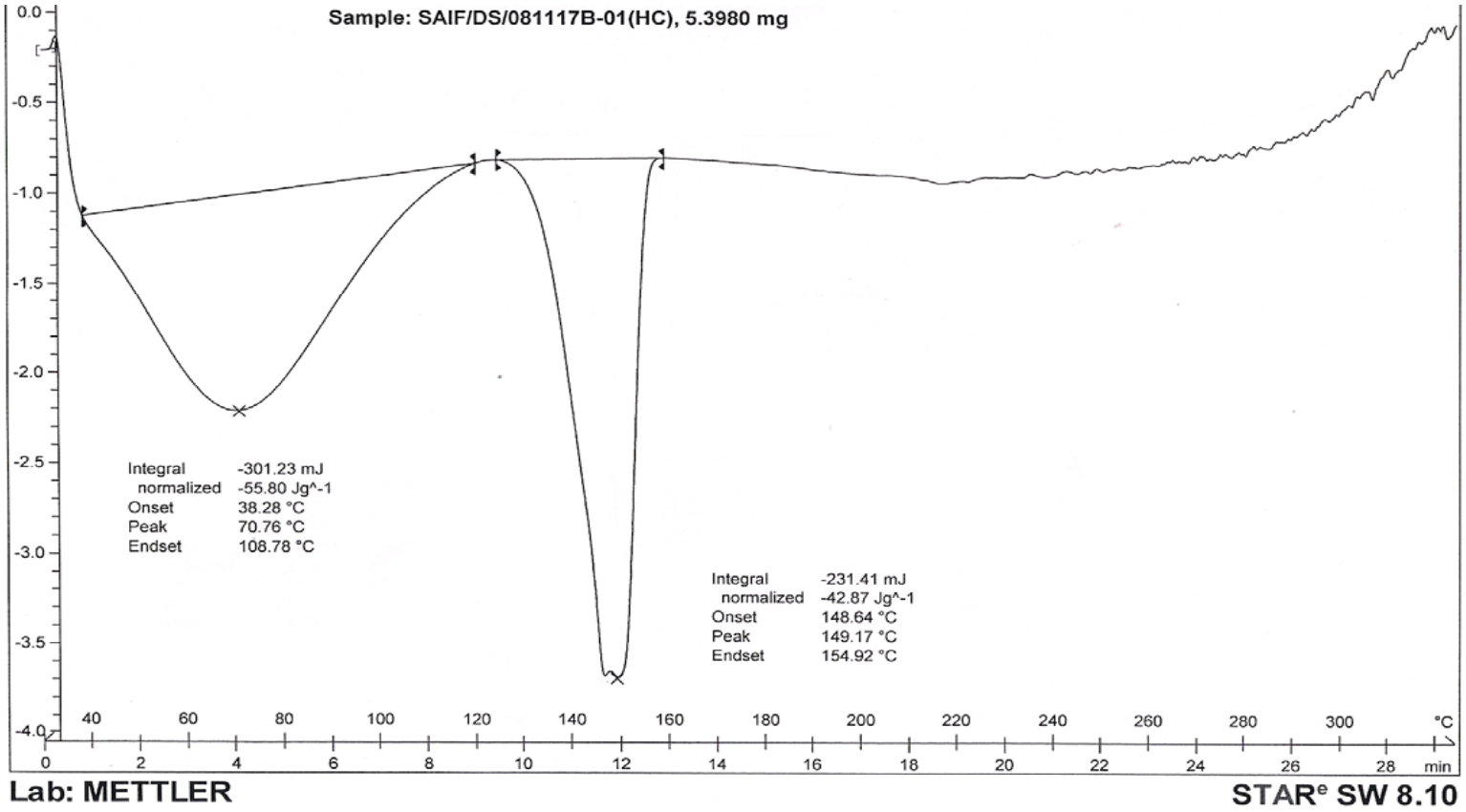


Figure no.14. DSC STUDIES OF INDOMETHACIN SOLID DISPERSION WITH HPβ-CD 1:1 (KNEADING METHOD)

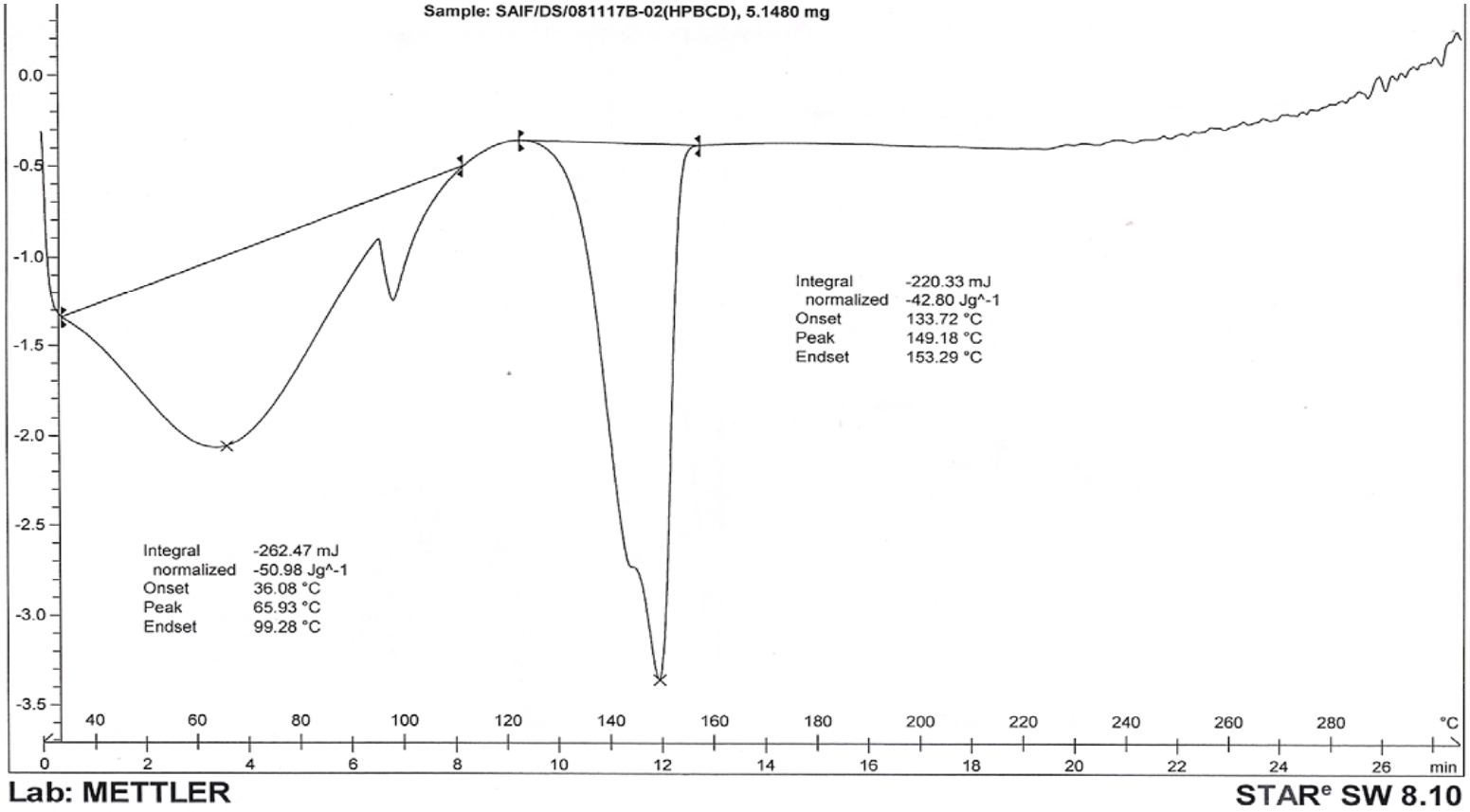


Figure no.15. DSC STUDIES OF INDOMETHACIN SOLID DISPERSION WITH β-CD AND HPβ-CD 1:1 (KNEADING METHOD)

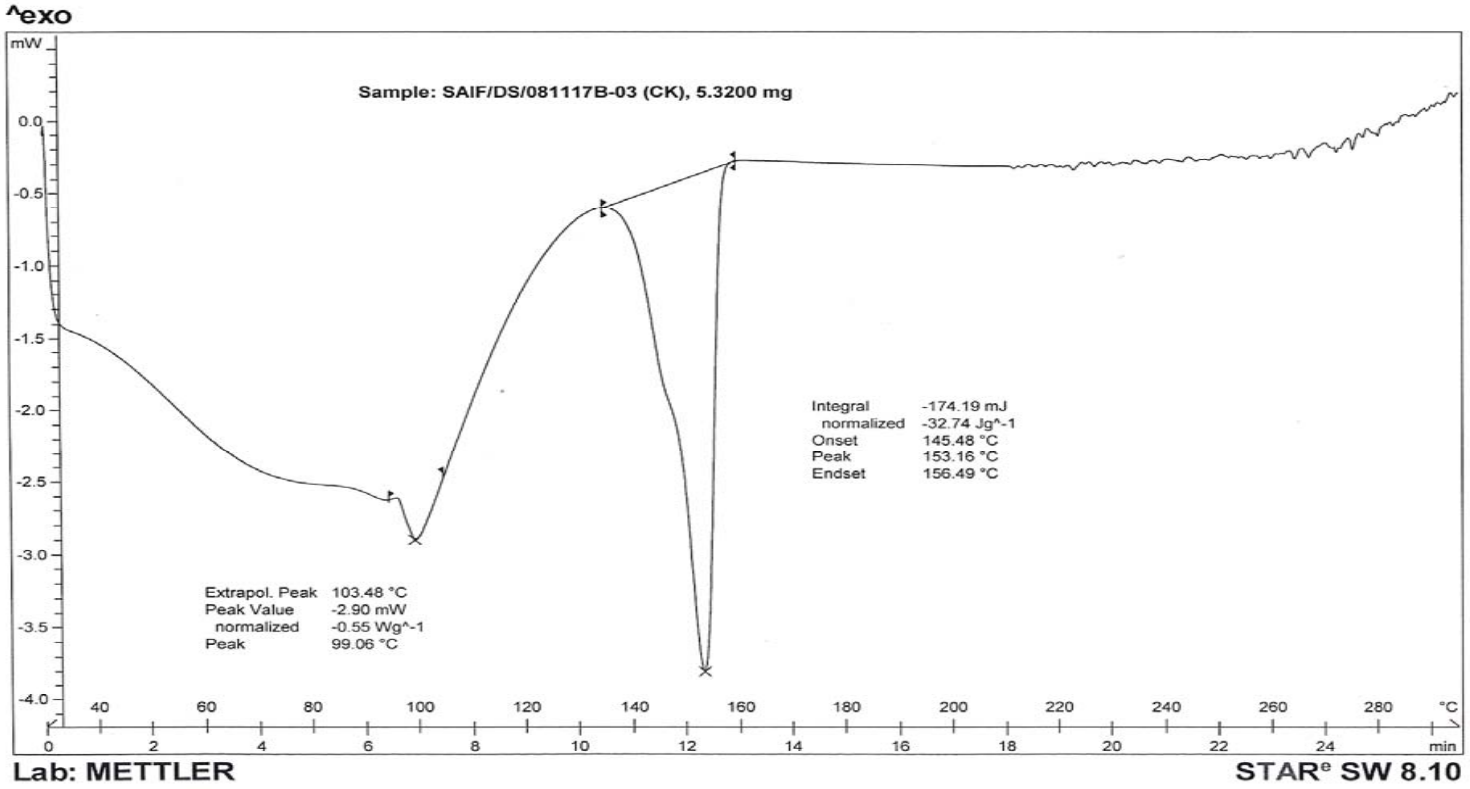


Figure no.16. DSC STUDIES OF INDOMETHACIN SOLID DISPERSION WITH β-CD 1:1 (KNEADING METHOD)

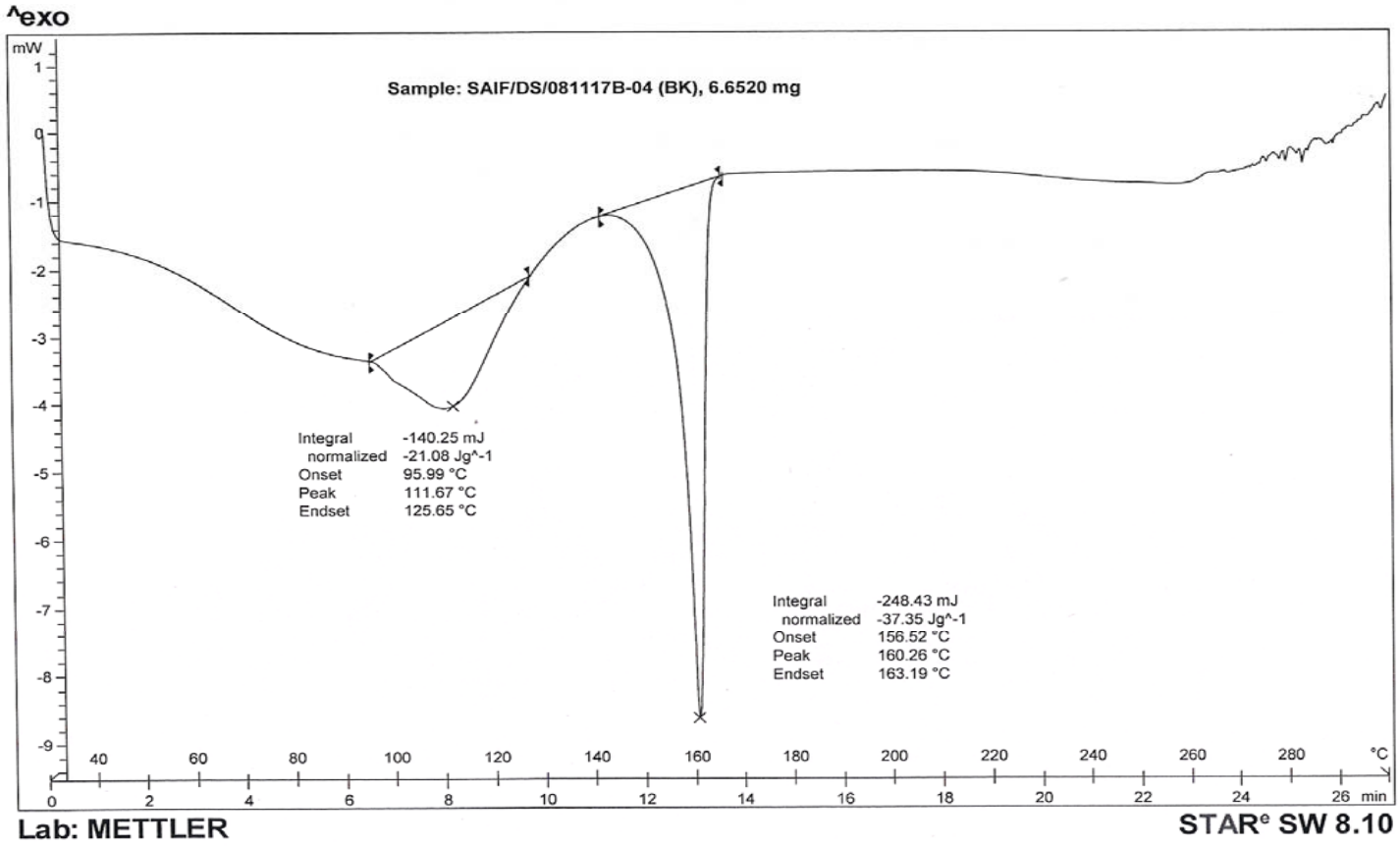
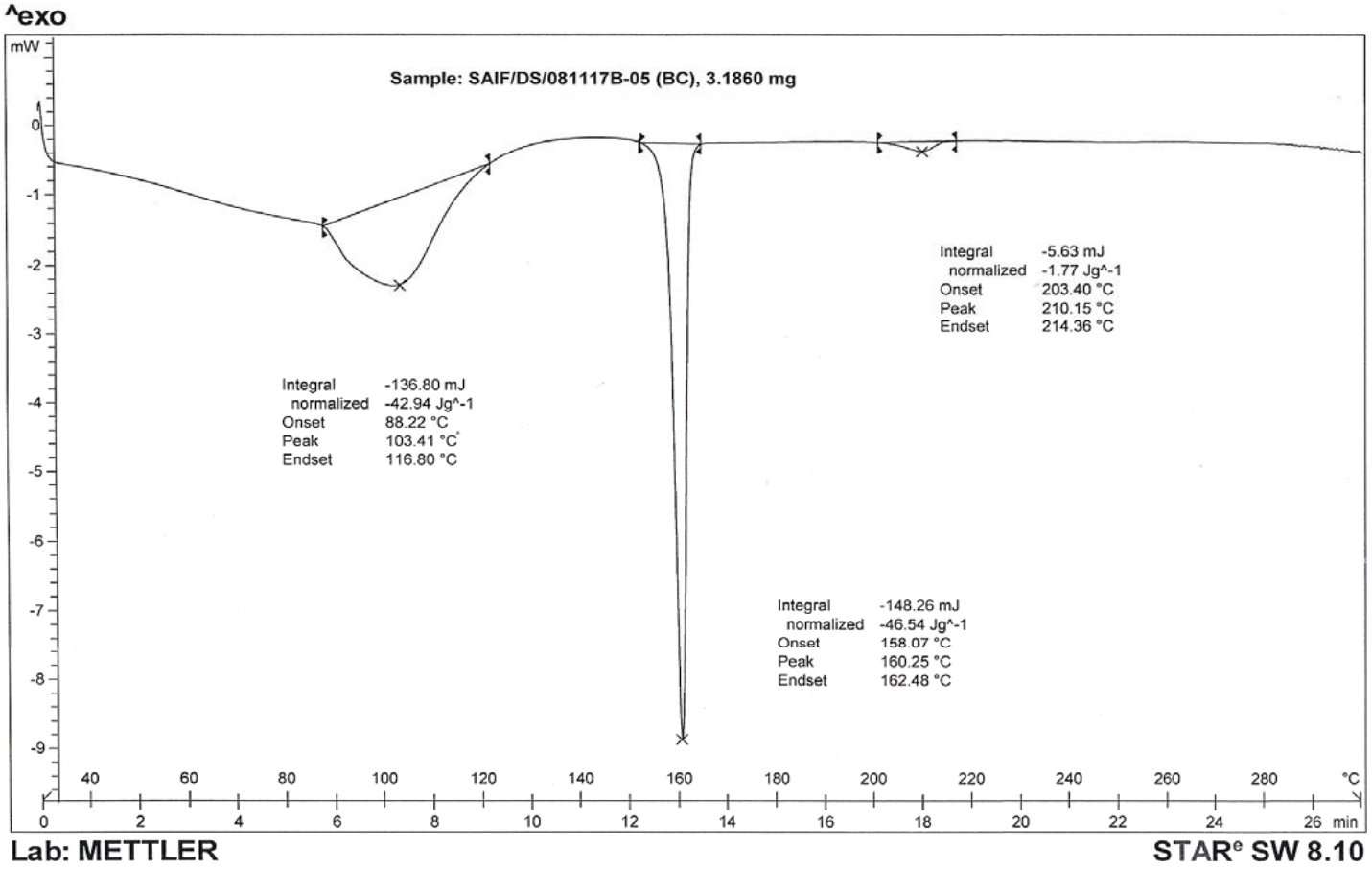


Figure no.17. DSC STUDIES OF INDOMETHACIN SOLID DISPERSION WITH β-CD 1:1 (CO-EVAPORATION METHOD)



IN-VITRO DISSOLUTION STUDIES OF DIFFERENT SOLID DISPERSIONS OF INDOMETHACIN

The dissolution studies are the most important part of the evaluation of a solid dispersion, where the dissolution of pure drug and solid dispersion is carried out. Dissolution rate studies of various solid dispersions were carried out in 0.1M pH 7.2 phosphate buffer using XXII dissolution rate apparatus (Electrolab). Which are shown in tables 6-14 and figures 18-24.

DISSOLUTION METHOD

900 ml of 0.1M pH 7.2 phosphate buffer was used as dissolution medium. Solid dispersions equivalent to 100 mg of Indomethacin was taken in hard gelatin capsule; a stainless steel wire was wound around the capsule as a sink. The paddle type stirrer was adjusted to 100 rpm. The temperature was maintained at 37.4^0C, 5 ml of aliquot dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The samples were analyzed for Indomethacin after suitable dilution by measuring absorbance at 320nm using JASCO V-530UV-Visible spectrophotometer. 0.1M pH 7.2 phosphate buffer was used as a blank. The percentage of Indomethacin dissolved at various time intervals was calculated and plotted against time.

Table no : 6 DISSOLUTION PROFILE OF INDOMETHACIN IN PURE FORM,PHYSICAL MIXTURE AND FROM SOLID DISPERSIONS PREPARED BY CO-EVAPORATION METHOD CONTAINING β-CYCLODEXTRIN AT DIFFERENT DRUG:CARRIER RATIOS

Time in min	Percentage of indomethacin dissolved from				
	Pure drug	PM	1:1	1:3	1:9
5	2.25	1.125	2.65	10.87	9.15
10	8.12.	2.27	5.75	19.85	18.175
15	15.75	7.05	10.82	33.75	25.17
30	24.12	12.375	27.85	65.75	41.55
45	30.42	39.5	59.17	70.85	74.85
60	39.17	61.75	72.75	78.12	83.12

Table no : 7 DISSOLUTION PROFILE OF INDOMETHACIN IN PURE FORM, PHYSICAL MIXTURE AND FROM SOLID DISPERSIONS PREPARED BY KNEADING TECHNIQUE CONTAINING β-CYCLODEXTRIN AT DIFFERENT DRUG:CARRIER RATIOS

Time in min	Percentage of indomethacin dissolved from				
	Pure drug	PM	1:1	1:3	1:9
5	2.25	1.125	2.75	2.75	5.25
10	8.12.	2.27	4.25	4.87	9.15
15	15.75	7.05	10.12	14.5	20.02
30	24.12	12.375	24.62	29.25	39.12
45	30.42	39.5	48.5	56.25	65.25
60	39.17	61.75	76.5	78.92	89.12

Table no : 8 DISSOLUTION PROFILE OF INDOMETHACIN IN PURE FORM PHYSICAL MIXTURE AND FROM SOLID DISPERSIONS PREPARED BY CO-EVAPORATION METHOD CONTAINING HPβ-CD AT DIFFERENT DRUG:CARRIER RATIOS

Time in min	Percentage of indomethacin dissolved from				
	Pure drug	PM	1:1	1:3	1:9
5	2.25	10.125	2.25	2.25	2.15
10	8.12.	14.72	5.15	9.25	4.37
15	15.75	21.23	15.75	13.15	21.15
30	24.12	41.035	25.75	25.42	37.15
45	30.42	51.025	54.15	45.75	61.37
60	39.17	78.08	67.87	72.62	81.32

Table no.9. DISSOLUTION PROFILE OF INDOMETHACIN IN PURE FORM AND FROM SOLID DISPERSIONS PREPARED BY KNEADING TECHNIQUE CONTAINING HPβ-CD AT DIFFERENT DRUG:CARRIER RATIOS

Time in min	Percentage of indomethacin dissolved from				
	Pure drug	PM	1:1	1:3	1:9
5	2.25	10.125	10.125	6.75	4.25
10	8.12.	14.72	14.72	17.12	13.5
15	15.75	21.23	21.23	50.47	33.15
30	24.12	41.035	41.035	59.125	42.75
45	30.42	51.025	51.025	73.25	78.75
60	39.17	78.08	78.08	85.5	91.75

Table no : 10 DISSOLUTION PROFILE OF INDOMETHACIN IN PURE FORM AND FROM SOLID DISPERSIONS PREPARED WITH VARIOUS CARRIERS AT DRUG:CARRIER RATIO 1:1

Time in min	Dissolution of indomethacin from various solid dispersions at drug : carrier ratio 1:1					
	Pure drug	β-CD CO	β-CD KM	HPβ-CD CO	HPβ-CD KM	Combination of β-CD & HPβ-CD
5	2.25	2.65	2.75	2.25	10.125	2.25
10	8.12.	5.75	4.25	5.15	14.72	7.75
15	15.75	10.82	10.12	15.75	21.23	29.27
30	24.12	27.85	24.62	25.75	41.035	35.75
45	30.42	59.17	48.5	54.15	51.025	69.27
60	39.17	72.75	76.5	67.87	78.08	76.75

Table no.11 DISSOLUTION PROFILE OF INDOMETHACININ PURE FORM AND FROM SOLID DISPERSIONS PREPARED WITH VARIOUS CARRIERS AT DRUG:CARRIER RATIO 1:3

Time in min	Dissolution of indomethacin from various solid dispersions at drug : carrier ratio 1:3					
	Pure drug	β-CD CO	β-CD KM	HPβ-CD CO	HPβ-CD KM	Combination of β-CD & HPβ-CD
5	2.25	10.87	2.75	2.25	6.75	2.65
10	8.12.	19.85	4.87	9.25	17.12	8.75
15	15.75	33.75	14.5	13.15	50.47	27.27
30	24.12	65.75	29.25	25.42	59.125	37.17
45	30.42	70.85	56.25	45.75	73.25	59.17
60	39.17	78.12	78.92	72.62	85.5	77.25

Table no : 12 DISSOLUTION PROFILE OF INDOMETHACIN IN PURE FORM AND FROM SOLID DISPERSIONS PREPARED WITH VARIOUS CARRIERS AT DRUG: CARRIER RATIO 1:9

Time in min	Dissolution of indomethacin from various solid dispersions at drug : carrier ratio 1:9					
	Pure drug	β-CD CO	β-CD KM	HPβ-CD CO	HPβ-CD KM	Combination of β-CD & HPβ-CD
5	2.25	9.15	5.25	2.15	4.25	4.75
10	8.12.	18.175	9.15	4.37	13.5	10.475
15	15.75	25.17	20.02	21.15	33.15	33.75
30	24.12	41.55	39.12	37.15	42.75	42.175
45	30.42	74.85	65.25	61.37	78.75	54.75
60	39.17	83.12	89.12	81.32	91.75	80.175

Table no : 13 PERCENTAGE RELEASE OF INDOMETHACIN FROM VARIOUS SOLID DISPERSIONS

Time In Min	percentage of Indomethacin released from																	
	Pure drug	With HPβ-CD							With β-CD							Combination of β-CD & HPβ-CD(kneading)		
		PM	Co-evaporation method			Kneading method			PM	Co-evaporation method			Kneading method					
		1:1	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:1	1:3	1:9	1:1	1:3	1:9	1:1	1:3	1:9
5	2.25	10.125	2.25	2.25	2.15	10.125	6.75	4.25	1.125	2.65	10.87	9.15	2.75	2.75	5.25	2.25	2.65	4.75
10	8.12.	14.72	5.15	9.25	4.37	14.72	17.12	13.5	2.27	5.75	19.85	18.175	4.25	4.87	9.15	7.75	8.75	10.475
15	15.75	21.23	15.75	13.15	21.15	21.23	50.47	33.15	7.05	10.82	33.75	25.17	10.12	14.5	20.02	29.27	27.27	33.75
30	24.12	41.035	25.75	25.42	37.15	41.035	59.125	42.75	12.375	27.85	65.75	41.55	24.62	29.25	39.12	35.75	37.17	42.175
45	30.42	51.025	54.15	45.75	61.37	51.025	73.25	78.75	39.5	59.17	70.85	74.85	48.5	56.25	65.25	69.27	59.17	54.75
60	39.17	78.08	67.87	72.62	81.32	78.08	85.5	91.75	61.75	72.75	78.12	83.12	76.5	78.92	89.12	76.75	77.25	80.175

Table no .14 FIRST ORDER RATE CONSTANTS FOR INDOMETHACIN FROM VAROIUS SOLID DISPERSIONS

SOLID DISPERSION	K(MIN-1)
INDOMETHACIN	0.036
INDOMETHACIN:HPB-CD	
PHYSICAL MIXTURE	0.00222
1:1	0.0179
1:3	0.0181
1:9	0.0238
INDOMETHACIN:B-CD(CO)	
PHYSICAL MIXTURE	0.009198
1:1	0.0201
1:3	0.020
1:9	0.0349
INDOMETHACIN: B-CD(KM)	
PHYSICAL MIXTURE	0.009543
1:1	0.0178
1:3	0.0154
1:9	0.022

RESULTS AND DISCUSSION

Solid dispersions of Indomethacin was prepared with polymer β-Cyclodextrin and HPβ-CD using kneading and co-evaporation methods, were found to be free flowing powder. Characterization of solid dispersion was done by TLC, IR spectral analysis, X-Ray diffraction and differential scanning calorimetry.

Thin layer chromatography

Solid dispersions of Indomethacin gave a single spot corresponding to Indomethacin pure drug. Similar Rf values were obtained for pure drug and solid dispersions of Indomethacin. TLC studies thus indicated no interactions between drug and the carriers in the solid dispersions prepared.

FT - IR spectral studies

The solid dispersions of Indomethacin and pure drug were studied for IR analysis. Identical IR spectrums were obtained for pure drug and solid dispersions. This confirmed the absence of any chemical interaction between drug and the carrier

X-Ray diffraction

Patterns of pure drug showed intensive peaks indicating the crystalline nature of Indomethacin, which is reduced in solid dispersions where the peaks indicate the amorphous nature of Indomethacin, which might be the reason for improved dissolution characteristics of solid dispersions.

Differential scanning calorimetry

DSC thermogram of Indomethacin from all solid dispersions shows that there was no interaction between the drug and the carrier used and amorphous character of the drug in the solid dispersions.

Dissolution studies

Dissolution rate of Indomethacin from all solid dispersions was found to be increased when compared to the physical mixture and pure Indomethacin. The dissolution of solid dispersions followed first order kinetics. The solid dispersions with both the cyclodextrins, at the ratio of 1:9 (drug: carrier) exhibited the highest rate of dissolution and moreover the solid dispersion prepared by complexation exhibited the highest dissolution rate and efficiency than those prepared by kneading method.

The drug release from the solid dispersion after 30 minutes of dissolution for the ratio of 1:9 was more than 50% where as for the physical mixture and pure drug it was around 30%.

SUMMARY AND CONCLUSION

Indomethacin solid dispersions were prepared using carriers such as β-CD and HPβ-CD. In this present study the solid dispersions were prepared by Co-evaporation for both the polymers and kneading method for β-CD and HPβ-CD.

The solid dispersions prepared were found to be free flowing powders. In TLC studies single spots appeared for pure drug and solid dispersions shows that there was no interaction between the drug and the carrier used.

The IR spectra obtained for the solid dispersions were matching with reference standards. This indicates that the drug was pure and the spectra obtained from solid dispersions were matching with the original spectra. No characteristic peaks were disappeared or newly appeared which confirmed the absence of any chemical interaction between the drug and the carrier.

X-Ray diffraction studies revealed that the crystalline nature of Indomethacin in pure form was reduced in the solid dispersions and this might be the reason for increased dissolution rate.

DSC thermogram showed no interaction between drug and polymer. It also indicates the amorphous character of solid dispersion.

Results of dissolution studies showed rapid and fast dissolution of Indomethacin from all solid dispersions when compared with physical mixture and pure drug. The dissolution from all dispersions showed first order kinetics. Among two Cyclodextrins, HPβ-CD gave the faster dissolution.

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